รายงานวิจัยฉบับสมบูรณ์

การสังเคราะห์สารประเภทเตตระไฮโดรไพรานิลไดเอริลเฮพทานอยด์ที่มีฤทธิ์ต้านการเสื่อมของเซลล์ประสาท

(Synthesis of Anti-Neuroinflamatory Tetrahydropyranyl Diarylheptanoids)

ผู้ช่วยศาสตราจารย์ ดร. ขวัญฤทัย ธาตุเพ็ชร

ภาควิชาเคมี คณะวิทยาศาสตร์

โครงการวิจัยนี้ได้รับทุนสนับสนุนจากเงินรายได้มหาวิทยาลัย

มหาวิทยาลัยสงขลานครินทร์

ประจำปีงบประมาณ 2558 รหัสโครงการ SCI581192S

กิตติกรรมประกาศ

โครงการวิจัยเรื่องการสังเคราะห์สารประเภทเตตระไฮโดรไพรานิล ไดเอริลเฮพทานอยด์ที่มีฤทธิ์ต้านการเสื่อมของเซลล์ประสาท (Synthesis of Anti-Neuroinflammatory Tetrahydropyranyl-diarylheptanoids) นี้ได้รับทุนสนับสนุนจากงบประมาณเงินรายได้มหาวิทยาสงขลานครินทร์ ประจำปีงบประมาณ 2558 สัญญาเลขที่ SCI581192S ผู้วิจัยขอขอบคุณภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์สำหรับสถานที่ทำวิจัยและเครื่องมือวิจัยที่เกี่ยวข้อง

ขวัญฤทัย ธาตุเพ็ชร

กันยายน 2561

บทคัดย่อ

โครงการวิจัยนี้เป็นการสังเคราะห์สารประเภทเตตระไฮโดรไพรานิล ไดเอริลเฮพทานอยด์จำนวน 4 สารซึ่งแยกได้จาก *Disocorea villosa* โดยสารในกลุ่มนี้แสดงฤทธิ์ต้านการเสื่อมของเซลล์ประสาทและมีความเป็นพิษต่อเซลล์ดีต่ำ ปฏิกิริยาหลักที่ใช้ในการสังเคราะห์ ได้แก่ ปฏิกิริยา Prins cyclization เพื่อสร้างวงเตตระไฮโดรไพแรน ปฏิกิริยา Keck asymmetric allylation และปฏิกิริยา Mitsunobu เพื่อเปลี่ยนสเตอริโอเคมีสัมบูรณ์ของไครัลแอลกอฮอล์ นอกจากนี้ยังได้ทำการศึกษาสภาวะที่เหมาะสมของปฏิกิริยา Prins cyclization เพื่อลดการเกิด racemization ซึ่งงานวิจัยนี้สามารถยืนยันสเตอริโอเคมีสัมบูรณ์ของสารผลิตภัณฑ์ธรรมชาติทั้งสี่ได้อีกด้วย สารสังเคราะห์ทั้งสี่และสารอื่น ๆ ที่ได้ระหว่างการสังเคราะห์ถูกนำไปทดสอบฤทธิ์การต้านโรคเบาหวานและฤทธิ์ต้านเซลล์มะเร็งลำไส้ใหญ่ HT-29

Abstract

This research work involves concise syntheses of four tetrahydropyranyl diaryl-heptanoids isolated from *Disocorea villosa*. These natural products displayed anti-neuroinflammatory activity (inhibitory effect on nitric oxide production in LPS-activated murine microglia BV-2 cells) with low cell toxicity. The key synthetic features include Prins cyclization to construct the tetrahydropyran cores, Keck asymmetric allylation and Mitsunobu inversion. Optimization of the Prins cyclization conditions in order to minimize racemization has been described. Our syntheses also confirmed the absolute stereochemistry of the natural products. The four synthetic compounds and some synthetic intermediates were evaluated for antidiabetic activity via protective action against INS-1832/13 pancreatic β-cells through antiapoptosis as well as cytotoxic activity against human colorectal adenocarcinoma (HT-29) cell line.

บทสรุปผู้บริหาร (Executive Summary)

บทนำ

The diarylheptanoids are a group of plant secondary metabolites possessing the 1,7-diphenylheptane skeleton, which exhibit a wide range of biological properties such as anti-inflammatory, antioxidant, anticancer, antibacterial and antiosteoporotic activities. A subgroup of these diarylheptanoids are those possessing tetrahydropyran (THP) rings which have been shown to display interesting biological activities. In 2012, Chen and co-workers reported the isolation of five new cyclic diarylheptanoids containing THP cores (**1-5**) from the methanol extracts of the roots and rhizomes of *Dioscorea villosa* (wild yam) (Figure 1). The absolute configurations of **1-5** were proposed based on the Mosher's ester analysis. In 2013, Lee and co-workers disclosed the isolation of tetrahydropyranyl diarylheptanoids **1**, **3** and **5** from the rhizomes of *Dioscorea nipponica* along with two new tetrahydropyranyl diarylheptanoids, diosniponols A and B. In Lee's study, compounds **1, 3** and **5** displayed anti-neuroinflammatory activity (inhibitory effect on nitric oxide production in LPS-activated murine microglia BV-2 cells) with low cell toxicity. Further investigation on this group of compounds could be beneficial for drug discovery in neurodegenerative diseases such as Alzheimer's disease as well as other related diseases. Thus, this research work involved syntheses of four tetrahydropyranyldiarylheptanoids (**1-4**) in order to confirm the structures and the proposed absolute stereochemistry of the natural products as well as to further evaluate their biological activities.

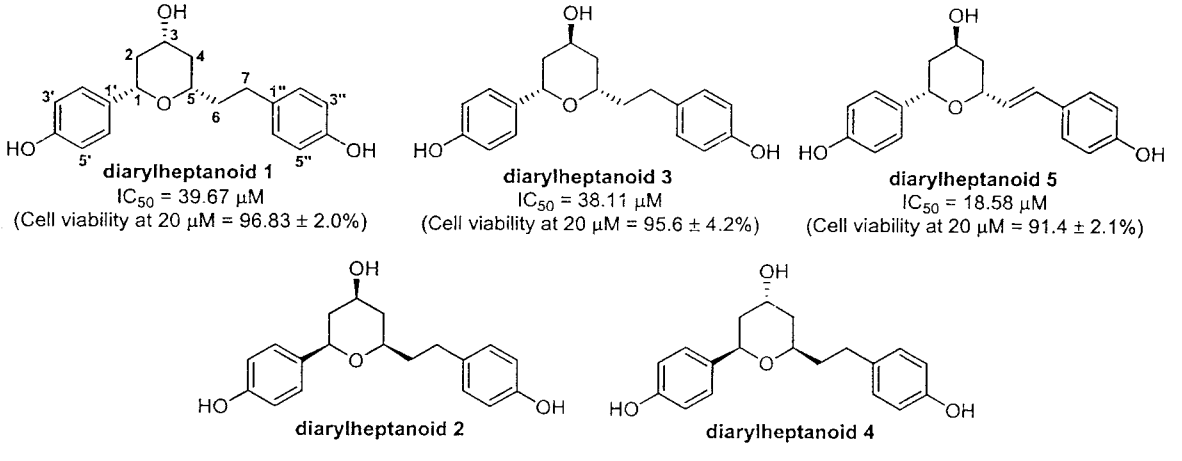


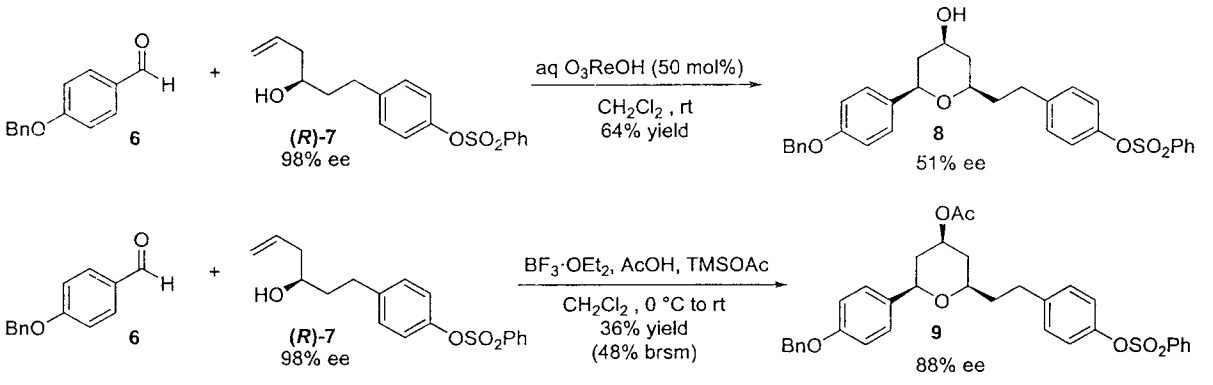
Figure 1. Tetrahydropyranyldiarylheptanoid isolated from *D. villosa* and *D. nipponica* and inhibitory effects on NO production in LPS-activated murine microglia BV-2 cells of diarylheptanoids **1**, **3** and **5**.

วัตถุประสงค์

To synthesize diarylheptanoids **1-4** in order to confirm the structures and the proposed absolute stereochemistry of the natural products as well as to further evaluate their biological activities

สรุป

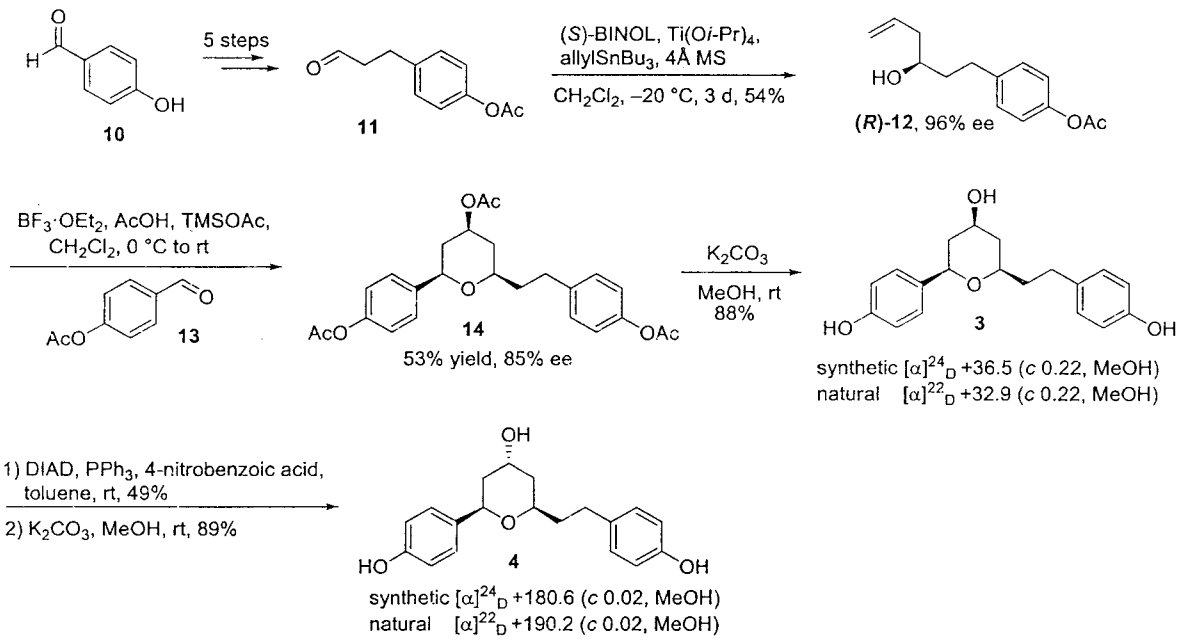
The synthesis of tetrahydropyranyl diarylheptanoids **1-4** has been accomplished utilizing the key Prins cyclization reaction of benzaldehyde and chiral homoallylic alcohol derivatives. The chiral homoallylic alcohol starting material was prepared using Keck asymmetric allylation to install the stereogenic center in high enantioselectivity. Original attempts were performed using perrhenic acid-catalyzed Prins cyclization reactions. Although the optimal O_3ReOH-catalyzed Prins cyclization could lead to the desired tetrahydropyran (THP) skeleton in good yield, the racemization occurred under these conditions and led to significant loss of enantiopurity in the product (Scheme 1). Therefore, different Prins cyclization conditions using trifluoroacetic acid (TFA) and $BF_3 \cdot OEt_2$ as acid promoters were investigated. TFA-mediated Prins cyclization reaction led to a messy reaction and a number of side products were observed. ThePrins cyclization reaction using a combination of $BF_3 \cdot OEt_2$, acetic acid (AcOH) and trimethylsilyl acetate (TMSOAc) led to the formation of the desired THP product in 36% yield (48% yield based on recovered starting material). To our delight, the $BF_3 \cdot OEt_2$-mediated conditions gave good enantiointegrity and resultedin a small loss of the optical purity (88% ee) of the desired THP product. We thus employed these optimal $BF_3 \cdot OEt_2$-mediated Prins cyclization conditions to complete the total synthesis of tetrahydropyranyl diarylheptanoids **1-4** with slight modification of protecting group to the acetyl (Ac) group for the purpose of increasing the product yield and reducing the number of synthetic steps.



Scheme 1. Prins cyclizations of benzaldehyde **6** and (*R*)-homoallylic alcohol **7** under O_3ReOH-catalyzed and $BF_3 \cdot OEt_2$-mediated conditions.

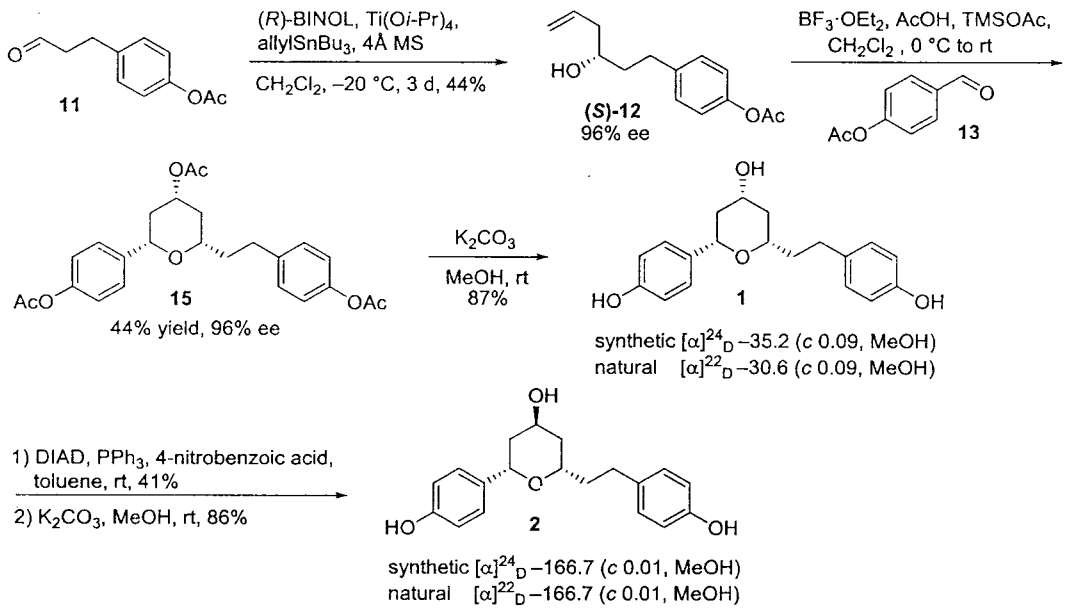
The synthesis of tetrahydropyranyldiarylheptanoids**1-4** is outlined in Schemes 2 and 3. Aldehyde **11**, which was a common intermediate required for the synthesis of chiral homoallylic alcohols (*R*)-**12** and (*S*)-**12**, was prepared in 5 steps from 4-hydroxybenzaldehyde (**10**). Keck allylation of **11** using (*S*)-BINOL and $Ti(O\textit{i}\text{-}Pr)_4$ catalysts furnished homoallylic alcohol (*R*)-**12** in 54% yield and 96% ee. Prins cyclization of (*R*)-**12** and 4-acetoxybenzaldehyde (**13**) under the established $BF_3 \cdot OEt_2$-mediated conditions gave the THP product **14** in 53% yield and 85% ee. Although the enantiopurity of the THP product obtained from these acetate-protected substrates was slightly lower than that of **9**, the product yield

was significantly higher and we selected these optimized substrates and reaction conditions to complete the synthesis of diarylheptanoid natural products **1-4**. Methanolysis of the three acetate groups of **14** using K_2CO_3 in methanol smoothly gave diarylheptanoid**3** in 80% yield. The spectroscopic data of **3** were identical to those of the natural product. The specific rotation of **3** was determined to be $[\alpha]^{24}_D$ +36.5 (*c* 0.22, MeOH) which was nearly identical to the specific rotation of the natural product ($[\alpha]^{22}_D$ +32.9 (*c* 0.22, MeOH)) and thus confirmed the absolute configurations of (1*R*,3*S*,5*R*) assigned to the natural product by Lee and co-workers. Diarylheptanoid **3** was subjected to Mitsunobu inversion, followed by methanolysis to give diarylheptanoid **4**. The specific rotation of **4** was determined to be $[\alpha]^{24}_D$ +180.6 (*c* 0.02, MeOH) which was in accordance with that of the natural product ($[\alpha]^{22}_D$ +190.2 (*c* 0.02, MeOH)) and thus confirmed the absolute configurations of (1*R*,3*R*,5*R*) assigned to the natural product.



Scheme 2. Preparation of (*R*)-homoallylic alcohol **12** and syntheses of **3** and **4**.

Syntheses of diarylheptanoids **1** and **2** were completed using the same synthetic sequence (Scheme 3). Keck allylation of **11** using (*R*)-BINOL and Ti(O*i*-Pr)$_4$ catalysts gave (*S*)-homoallylic alcohol precursor **12** in 44% yield and 96% ee. Prins cyclization of (*S*)-**12** and 4-acetoxybenzaldehyde (**13**) under the same $BF_3{\cdot}OEt_2$-mediated conditions gave the THP product **15** in 45% yield and 96% ee. Notably, the key Prins cyclization of (*S*)-**12** resulted in no loss of optical purity of the product. Following the same synthetic operations for **3** and **4**, methanolysis of **15** afforded diarylheptanoid **1** in 87% yield. Mitsunobu inversion of **1** and subsequent methanolysis smoothly furnished diarylheptanoid**2**. Spectroscopic data of both synthetic**1** and **2** were indistinguishable to those reported for the natural products. In addition, synthetic compounds **4** and **6** displayed nearly identical specific rotations to those of the natural products which confirmed their absolute configurations.



Scheme 3. Synthesis of the natural products **1** and **2**.

Synthetic compounds **1-4** and some synthetic intermediates were evaluated for antidiabetic activity via protective action against INS-1832/13 pancreatic β-cells through antiapoptosis as well as cytotoxic activity against human colorectal adenocarcinoma (HT-29) cell line. The protective activity assay against INS-1 832/13 pancreatic β-cells was performed by the laboratory of Professor Xu Shen, CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Shanghai, China. The cytotoxic activity against HT-29 cell line was performed using MTT assay by the laboratory of Assoc. Prof. Dr.Chatchai Muanprasat, Mahidol University, Thailand. For the INS-1 cells protection assay, it was observed that only diarylheptanoid **3** showed 71% protection rate at 20 μM whereas diarylheptanoids **1**,**2** and **4** were inactive. For the cytotoxic activity assay against HT-29 colon cancer cells, compounds **1-3** exhibited good cytotoxic activity (79%, 76% and 67%, respectively) while diarylheptonoid **4** show much lower cytotoxic activity against this cell line (29%). Nevertheless, some of the intermediates tested displayed significant and higher protection activity and cytotoxic activity against HT-29 cancer cell line compared to diarylheptanoids **1-4** (see Table 1 in Appendix).

ภาคผนวก

1. สำเนาบทความที่ได้รับการตีพิมพ์แล้ว (Reprint)

Tetrahedron Letters 57 (2016) 3505–3509

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of tetrahydropyranyl diarylheptanoids from *Dioscorea villosa*

Kawalee Kantee, Vatcharin Rukachaisirikul, Kwanruthai Tadpetch*

Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand

ARTICLE INFO

Article history:
Received 24 May 2016
Revised 13 June 2016
Accepted 22 June 2016
Available online 23 June 2016

Keywords:
Diarylheptanoids
Tetrahydropyran
Dioscorea villosa
Prins cyclization

ABSTRACT

Concise syntheses of four tetrahydropyranyl diarylheptanoids isolated from *Dioscorea villosa* have been described. The key features include Prins cyclization to construct the tetrahydropyran cores, Keck asymmetric allylation, and Mitsunobu inversion. Optimization of the Prins cyclization conditions in order to minimize racemization has been described. Our syntheses also confirmed the absolute stereochemistry of the natural products.

The diarylheptanoids are a group of plant secondary metabolites possessing the 1,7-diphenylheptane skeleton, which exhibit a wide range of biological properties such as anti-inflammatory, antioxidant, anticancer, antibacterial, and antiosteoporotic activities.[1] A subgroup of these diarylheptanoids are those possessing tetrahydropyran (THP) rings which have been shown to display interesting biological activities. Selected examples of this subgroup of diarylheptanoids are illustrated in Figure 1. Diospongin B (**1**), isolated from the rhizomes of *Dioscorea spongiosa*, shows promising inhibitory activity on bone resorption and could potentially be used as an antiosteoporotic drug.[2] Centrolobine (**2**), which was isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile*,[3] exhibits anti-inflammatory, antibacterial, and anti-leishmanial activities.[4] Additionally, rhoiptelol B (**3**), isolated from the fruits of *Rhoiptelea chiliantha*[5] and the bark of *Alnus hirsuta*,[6] possesses inhibitory activity against lipopolysaccharide (LPS)-induced nuclear factor-κB (NF-κB) activation, nitric oxide (NO) and tumor necrosis factor alpha (TNF-α) production[7] and hypoxia-inducible factor-1 (HIF-1) in AGS cells.[6]

In 2012, Chen and co-workers reported the isolation of five new cyclic diarylheptanoids containing THP cores (**4**–**8**) from the methanol extracts of the roots and rhizomes of *Dioscorea villosa* (wild yam) (Fig. 2).[8] The absolute configurations of **4**–**8** were proposed based on the Mosher's ester analysis. In 2013, Lee and co-workers disclosed the isolation of tetrahydropyranyl diarylheptanoids **4**, **6** and **8** from the rhizomes of *Dioscorea nipponica* along with two new tetrahydropyranyl diarylheptanoids, diosniponols A and B.[9] In Lee's study, compounds **4**, **6** and **8** displayed anti-neuroinflammatory activity (inhibitory effect on NO production in LPS-activated murine microglia BV-2 cells) with low cell toxicity. Further investigation on this group of compounds could be beneficial for drug discovery in neurodegenerative diseases such as Alzheimer's disease as well as other related diseases.

To date, there has been only one report regarding the synthesis of diarylheptanoid **5** by Yadav and co-workers (Scheme 1).[10] Their strategy to construct the 4-hydroxytetrahydropyran (4-OH THP) core relied on the selective hydrogenation and reduction of dihydropyrone **13**, which could be prepared from the aldol reaction between aldehyde **10** and acetophenone **11**. Diarylheptanoid **5** could be synthesized in 9 steps from aldehyde **9** in 20% overall yield.

The Prins cyclization reaction is a powerful synthetic transformation for constructing substituted THP rings[11] and has been utilized in a number of syntheses of natural products containing the 4-OH THP motif.[12] Typically, Prins cyclization reactions involve the acid-promoted coupling of aldehydes and homoallylic alcohols and proceed with high level of stereoselectivity favoring 2,4,6-*cis* THP rings.[13] Typical acids used include trifluoroacetic acid (TFA)[14] or a combination of BF_3-OEt_2 and acetic acid.[15] In 2008, Tadpetch and Rychnovsky reported a variation of the Prins cyclization reaction which was catalyzed by $O_3ReOSiPh_3$ or O_3ReOH as a convenient method to construct 4-OH THPs.[16] This protocol was highly effective with electron-rich aromatic aldehydes. In addition, both equatorial 4-OH and axial 4-OH products are possible using this catalytic system depending on the electronic nature of both

* Corresponding author. Tel.: +66 74 288437; fax: +66 74 558841.
E-mail address: kwanruthai.t@psu.ac.th (K. Tadpetch).

http://dx.doi.org/10.1016/j.tetlet.2016.06.102
0040-4039/

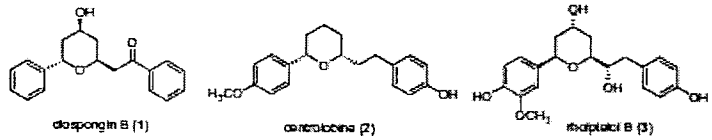


Figure 1. Selected biologically active tetrahydropyranyl diarylheptanoid natural products.

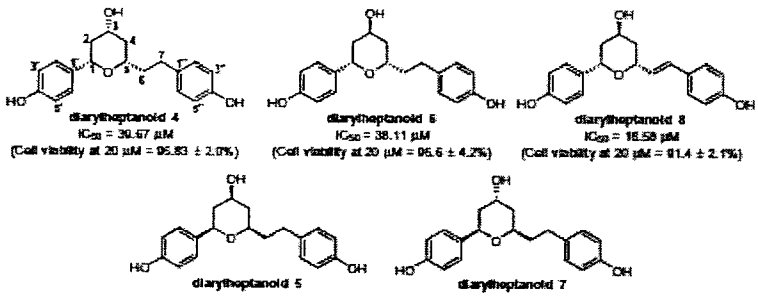
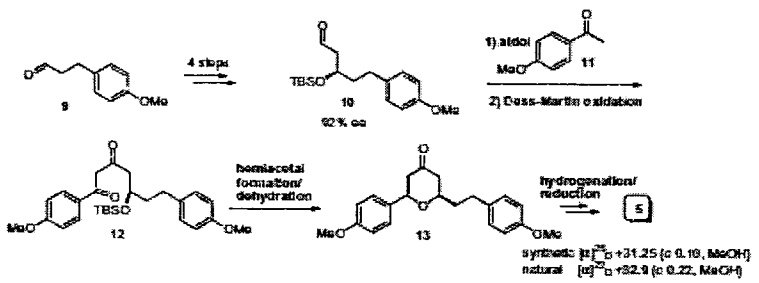
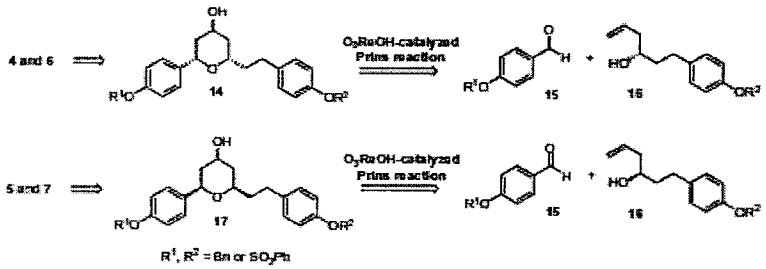


Figure 2. Tetrahydropyranyl diarylheptanoids isolated from *D. villosa* and *D. nipponica* and inhibitory effects on NO production in LPS-activated murine microglia BV-2 cells of diarylheptanoids **4**, **6** and **8**.



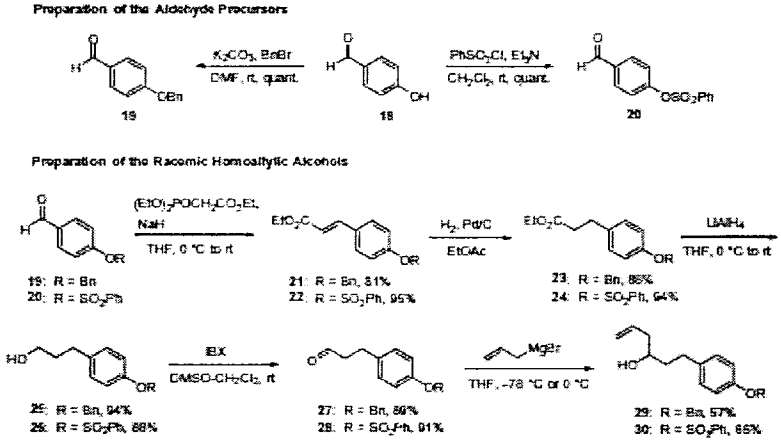
Scheme 1. Yadav's synthesis of diarylheptanoid 5.



Scheme 2. Retrosynthetic analysis of compounds 4–7.

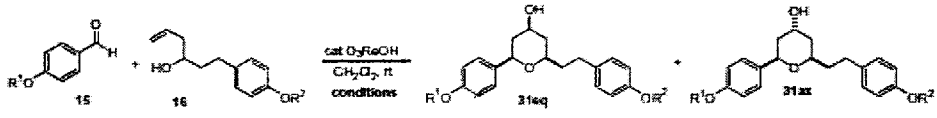
the aldehyde and homoallylic alcohol. Thus, it was envisioned that the desired natural products **4**–**7** could be prepared with this methodology from benzaldehyde derivative **15** and chiral homoallylic alcohol **16** utilizing the commercially available and easy-to-handle perrhenic acid (Scheme 2). Notably, the desired axial hydroxyl stereochemistry of compounds **6** and **7** would be directly accessed rather than the 2,4,6-*cis* stereoisomer typically obtained from the Prins reactions.

Our synthesis commenced with optimization of the reaction conditions using a racemic homoallylic alcohol precursor. Effects of the electronic properties of both substrates on the diastereoselectivity of the reaction were also investigated. It has been demonstrated by Rychnovsky and co-workers that the axial selectivity of nucleophilic trapping at the 4-position of the THP ring is a function of the lifetime and reactivity of the tetrahydropyranyl cation and the nucleophile, and could be tuned by altering the electronic properties of the substrates.[17] We thus investigated the effect of electron-donating and electron-withdrawing substituents (R^1 and R^2) on the reaction outcome. Benzyl (Bn) and benzenesulfonyl (SO_2Ph) protecting groups were chosen as representative electron-donating and electron-withdrawing groups, respectively.



Scheme 3. Preparation of the aldehyde and racemic homoallylic alcohol precursors.

Table 1
Screening O_3ReOH-catalyzed Prins cyclization conditions



Entry	R^1	R^2	Cat. loading (mol %)	Yield (%)	eq:ax
1	SO_2Ph	SO_2Ph	10	18	6.7:1
2	SO_2Ph	SO_2Ph	20	28	7.7:1
3	SO_2Ph	Bn	10	Trace	—
4	Bn	Bn	10	Trace	—
5	Bn	SO_2Ph	10	43	eq only
6	Bn	SO_2Ph	15	56	eq only
7	Bn	SO_2Ph	30	50	eq only
8	Bn	SO_2Ph	40	51	eq only
9	Bn	SO_2Ph	50	64	eq only
10	Bn	SO_2Ph	60	58	eq only
11	Bn	SO_2Ph	80	53	eq only
12	Bn	SO_2Ph	1 equiv	48	eq only

The synthesis of aldehyde and racemic homoallylic alcohol precursors for reaction optimization is described in Scheme 3. The benzaldehyde precursors were prepared by protection of the hydroxyl group of 4-hydroxybenzaldehyde (**18**) with a benzyl or a benzenesulfonyl group. Treatment of **18** with BnBr in the presence of K_2CO_3 in DMF at room temperature yielded 4-benzyloxybenzaldehyde (**19**) in quantitative yield, while 4-benzenesulfonyloxybenzaldehyde (**20**) was prepared in 83% yield by treating **18** with benzenesulfonyl chloride and Et_3N in CH_2Cl_2 at rt. Horner–Wadsworth–Emmons (HWE) reactions of aldehydes **19** and **20** using triethylphosphonoacetate and NaH gave α,β-unsaturated esters **21** and **22** in good yields. Hydrogenation of the alkene moiety in **21** and **22** using Pd/C in EtOAc furnished esters **23** and **24**, which after subjection to $LiAlH_4$ reduction delivered alcohols **25** and **26** in excellent yields. Oxidation of **25** and **26** with iodoxybenzoic acid (IBX) in DMSO–CH_2Cl_2 resulted in the formation of the corresponding aldehydes **27** and **28**. Treatment of **27** and **28** with allylmagnesium bromide yielded the desired racemic homoallylic alcohols **29** and **30** in 57% and 65% yield, respectively.

With the aldehyde and racemic homoallylic alcohol precursors in hand, we began investigating the effect of both substrates' protecting groups on product yields and stereoselectivity (Table 1). Reaction conditions using **10** mol % of the O_3ReOH catalyst in CH_2Cl_2 (0.1 M) at room temperature were initially chosen. When both R^1 and R^2 were electron-withdrawing groups (SO_2Ph), the reaction was very slow and low yields of the desired products were obtained; however, the axial 4-OH THP product (**31ax**) was observed as a minor product, while the expected equatorial 4-OH THP **31eq** was obtained as a major product (entry **1**). Increasing the catalyst loading to 20 mol % only slightly improved the product yield but the stereoselectivity for the formation of the axial 4-OH product decreased (entry 2). Changing the phenol protecting group on the homoallylic alcohol to an electron-donating group (Bn) led to trace amounts of the desired products and the major products observed were 4-OH THPs resulting from oxonia-Cope induced side-chain exchanges (entries 3 and 4) which was consistent with previous observations.[14a,18] When using an electron-rich aldehyde and an electron-withdrawing substituent on the homoallylic alcohol, the desired 4-OH THP product was obtained in 43% yield with complete equatorial stereoselectivity for nucleophilic trapping at the 4-position (entry 5). Increasing the catalyst loadings to **15**, 30 and 40 mol % led to moderately higher yields (entries 6–8). It was

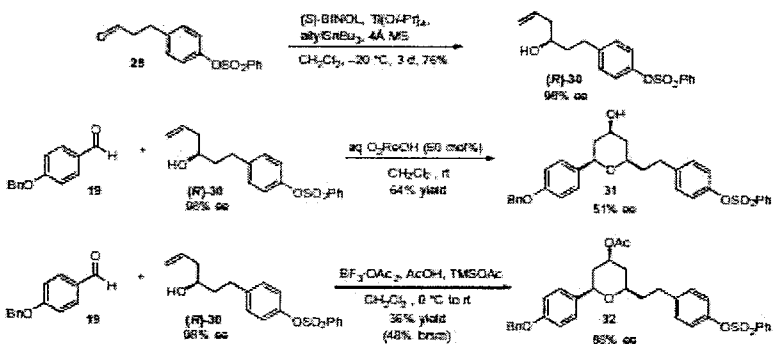
found that 50 mol % catalyst gave the highest yield of 64% (entry 9). Higher catalyst loadings of 60, 80 and 100 mol % seemed to diminish the yields (entries 10–12). We then chose benzaldehyde **19** and homoallylic alcohol **30** as the optimized substrates for further studies and decided that the stereochemistry of the alcohol stereogenic center at the 4-position would be inverted via a Mitsunobu reaction.

With optimized substrates and reaction conditions in hand, we proceeded to complete the natural product synthesis by using enantiopure homoallylic alcohols (Scheme 4). Keck asymmetric allylation[19] of aldehyde **28** using (*S*)-BINOL and $Ti(Oi\text{-}Pr)_4$ catalysts gave the (*R*)-homoallylic alcohol precursor **30** in 76% yield and 98% ee as determined by chiral HPLC. The absolute configuration of the newly generated stereogenic center was confirmed by Mosher's method.[20] Prins cyclization of (*R*)-**30** and 4-benzyloxybenzaldehyde (**19**) using 50 mol % O_3ReOH catalyst in CH_2Cl_2 at room temperature smoothly provided the desired (2*S*,4*R*,6*S*)-THP product **31** in 64% yield. The enantiopurity of **31** was determined by chiral HPLC analysis of its acetate derivative (**32**) to be 51% ee which indicated the significant loss of enantiopurity resulting from racemization which is a very common side-reaction of Prins cyclization reactions. Next, different Prins cyclization conditions utilizing TFA and $BF_3{\cdot}OEt_2$ as acid promoters were investigated. Prins cyclization of (*R*)-**30** and benzaldehyde **19** in the presence of TFA resulted in a messy reaction and a number of side-products were observed. However, the Prins cyclization reaction of (*R*)-**30** and benzaldehyde **19** using a combination of $BF_3{\cdot}OEt_2$, AcOH and TMSOAc as a fluoride trap in CH_2Cl_2[21] led to much cleaner reaction compared to that using TFA and the all-*cis* THP product **32** was obtained in 36% yield (48% yield based on recovered (*R*)-**30**). To our delight, the optical purity of THP product **32** was observed to be 88% ee. Although the $BF_3{\cdot}OEt_2$-mediated conditions gave good enantiointegrity, the product yield was diminished compared to that of the O_3ReOH-catalyzed conditions. Additionally, three different protecting groups had to be removed in order to complete the natural product. Thus, use of the same protecting group for the phenol moieties of both substrates would be advantageous to reduce the synthetic steps. We decided to use the acetate protecting groups on both substrates as Willis and co-workers had successfully utilized this protecting group in the synthesis of a novel tetrahydropyranyl diarylheptanoid isolated from *Zingiber officinale*.[21]

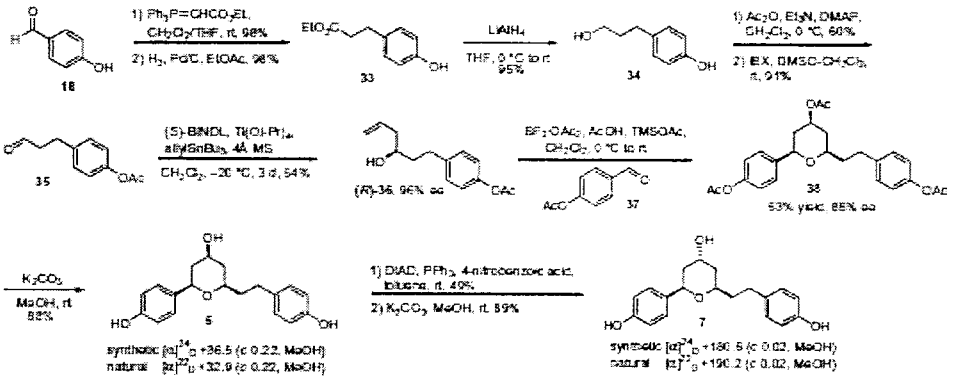
Synthesis of (*R*)-homoallylic alcohol **36** was achieved in a similar fashion to that of (*R*)-**30** with slight modification (Scheme 5). Wittig olefination of 4-hydroxybenzaldehyde (**18**) with (carbethoxymethylene)triphenylphosphorane, followed by hydrogenation of the resulting α,β-unsaturated ester gave ester **33** in excellent yields. Reduction of the ester functional group of **33** using $LiAlH_4$ furnished diol **34** in 95% yield. Selective protection of the phenol group of **34** using 0.5 equiv of Ac_2O in the presence of Et_3N and catalytic DMAP delivered the monoacetylated product in 60% yield, which upon subjection to IBX oxidation gave aldehyde **35** in 91% yield. Keck allylation of **35** using (*S*)-BINOL and $Ti(Oi\text{-}Pr)_4$ catalysts gave (*R*)-homoallylic alcohol precursor **36** in 54% yield and 96% ee. Prins cyclization of (*R*)-**36** and 4-acetoxybenzaldehyde (**37**) under the established $BF_3{\cdot}OEt_2$-mediated conditions gave the THP product **38** in 53% yield and 85% ee. Although the enantiopurity of the THP product obtained from these acetate-protected substrates was slightly lower than that of **32**, the product yield was significantly higher and we selected these optimized substrates and reaction conditions to complete the synthesis of diarylheptanoid natural products **4**–**7**. Methanolysis of the three acetate groups of **38** using K_2CO_3 in methanol smoothly gave diarylheptanoid **5** in 80% yield. The spectroscopic data of **5** were identical to those of the natural product. The specific rotation of **5** was determined to be $[\alpha]_D^{24}$ +36.5 (*c* 0.22, MeOH) which was nearly identical to the specific rotation of the natural product ($[\alpha]_D^{22}$ +32.9 (*c* 0.22, MeOH)) and thus confirmed the absolute configurations of (1*R*,3*S*,5*R*) assigned to the natural product by Lee and co-workers. Diarylheptanoid **5** was subjected to Mitsunobu inversion, followed by methanolysis to give diarylheptanoid **7**. The specific rotation of **7** was determined to be $[\alpha]_D^{24}$ +180.6 (*c* 0.02, MeOH) which was in accordance with that of the natural product ($[\alpha]_D^{22}$ +190.2 (*c* 0.02, MeOH)) and thus confirmed the absolute configurations of (1*R*,3*R*,5*R*) assigned to the natural product.

Syntheses of diarylheptanoids **4** and **6** were completed using the same synthetic sequence starting from (*S*)-homoallylic alcohol **36** (Scheme 6). Keck allylation of **35** using (*R*)-BINOL and $Ti(Oi\text{-}Pr)_4$ catalysts gave (*S*)-homoallylic alcohol precursor **36** in 44% yield and 96% ee. Prins cyclization of (*S*)-**36** and 4-acetoxybenzaldehyde (**37**) under the same $BF_3{\cdot}OEt_2$-mediated conditions gave the THP product **39** in 45% yield and 96% ee. Notably, the key Prins cyclization of (*S*)-**36** resulted in no loss of optical purity of the product. Following the same synthetic operations for **5** and **7**, methanolysis of **39** afforded diarylheptanoid **4** in 87% yield. Mitsunobu inversion of **4** and subsequent methanolysis smoothly furnished diarylheptanoid **6**. Spectroscopic data of both **4** and **6** were indistinguishable to those reported for the natural products. In addition, synthetic compounds **4** and **6** displayed nearly identical specific rotations to those of the natural products which confirmed their absolute configurations.

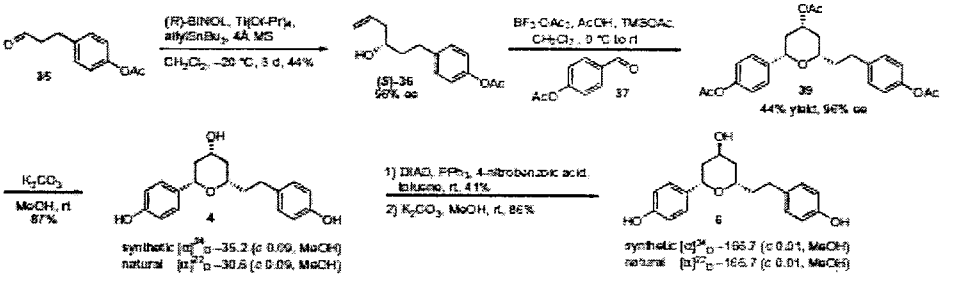
In conclusion, we report concise syntheses of four diarylheptanoids containing THP cores which were previously isolated from *Dioscorea villosa* and *Dioscorea nipponica*. The key features of the syntheses include Prins cyclization to construct the THP cores as well as Keck asymmetric allylation and Mitsunobu inver-



Scheme 4. Prins cyclizations of (*R*)-homoallylic alcohol **30** and aldehyde **19** under O_3ReOH-catalyzed and $BF_3{\cdot}OEt_2$-mediated conditions.



Scheme 5. Preparation of (*R*)-homoallylic alcohol **36** and syntheses of **5** and **7**.



Scheme 6. Synthesis of the natural products **4** and **6**.

sion. Investigation of the Prins cyclization conditions in order to minimize racemization has been described. Our syntheses also confirmed the absolute stereochemistry of the natural products **4–7**.

Acknowledgements

This work was supported by Prince of Songkla University (Grant No. SCI581192S). K. Kantee thanks the Faculty of Science Research Fund, Prince of Songkla University for research assistantship (Contract No. 1-2557-02-002). The Graduate School, Prince of Songkla University and the Center of Excellence for Innovation in Chemistry (PERCH-CIC) are acknowledged for partial support. We thank Dr. Thitima Rujiralai for assistance in HPLC experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.102.

References and notes

1. Lv, H.; She, G. *Rec. Nat. Prod.* **2012**, *6*, 321–333.
2. Yin, J.; Kouda, K.; Tezuka, Y.; Tran, Q. L.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, *70*, 54–58.
3. (a) Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1984**, *37*, 1127–1133; (b) de, C.; Alcántara, A. F.; Souza M. R.; Pilo-Veloso, D. *Fitoterapia* **2000**, *71*, 613–615.
4. (a) Aragão Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869–1875; (b) Araujo, C. A. C.; Alegrio, L. V.; Leon, L. L. *Phytochemistry* **1998**, *49*, 751–754.
5. Jiang, Z. H.; Tanaka, T.; Hirata, H.; Fukuoka, R.; Kouno, I. *Phytochemistry* **1998**, *47*, 1049–1054.
6. Jin, W. Y.; Cui, X. F.; Na, M. K.; Lee, J. J.; Bae, K. H. *Arch. Pharm. Res.* **2007**, *30*, 412–418.
7. Jin, W. Y.; Cui, X. F.; Na, M. K.; Lee, J. J.; Bae, K. H. *Biol. Pharm. Bull.* **2007**, *30*, 810–813.
8. Dong, S.-H.; Nikolić, D.; Simmler, C.; Qiu, F.; van Breemen, R. B.; Soejarto, D. D.; Pauli, G. F.; Chen, S.-N. *J. Nat. Prod.* **2012**, *75*, 2168–2177.
9. Woo, K. W.; Moon, E.; Kwon, O. W.; Lee, S. O.; Kim, S. Y.; Choi, S. Z.; Son, M. W.; Lee, K. R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3806–3809.
10. Yadav, J. S.; Gyanchander, E.; Bujjaranjpalli, S.; Das, S. *Tetrahedron Lett.* **2015**, *56*, 1360–1362.
11. For reviews on Prins cyclization reactions, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505–555; (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661–672; (c) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925–957; (d) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445.
12. For examples, see: (a) Lee, S. K.; Lee, E. *J. Am. Chem. Soc.* **2010**, *132*, 4564–4565; (b) Balmond, E. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181; (c) Vintonyak, V. V.; Maier, M. E. *Org. Lett.* **2008**, *10*, 1239–1242; (d) Seiden, P. T.; Charmant, J. P. H.; Willis, C. L. *Org. Lett.* **2008**, *10*, 1637–1640; (e) Wender, P. A.; DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658–6659.
13. General numbering of tetrahydropyran rings.
14. (a) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, C. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429–2432; (b) Yadav, J. S.; Singh, V. K.; Thirupathaiah, B.; Bal Reddy, A. *Tetrahedron Lett.* **2014**, *55*, 4427–4429.
15. (a) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679–8682; (b) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679–4686.
16. Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4839–4842.
17. Jasti, R.; Vitale, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904–9905.
18. (a) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815–3818; (b) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919–3922.
19. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
20. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519; (b) Hoye, T. R.; Jeffery, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458.
21. Parker, C. D.; Seiden, P. T.; Willis, C. L. *Tetrahedron Lett.* **2009**, *50*, 3686–3689.

Supplementary Data

Synthesis of tetrahydropyranyldiarylheptanoids from *Dioscoreavillosa*

KawaleeKantee, VatcharinRukachaisirikul, KwanruthaiTadpetch*

Department of Chemistry and Center for Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand.

* Corresponding author. Tel.: +66 74 288437; fax: +66 74 558841.
Email address: kwanruthai.t@psu.ac.th (K. Tadpetch).

List of Supplementary Data

1. General Information

Unless otherwise stated, all reactions were performed under an argon atmosphere in oven- or flamed-dried glassware. Solvents were used as received from suppliers or distilled prior to use using standard procedures. All other reagents were obtained from commercial sources and used without further purification. Column chromatography was performed on SiliaFlash® G60 Silica (60-200 μm, Silicycle) or Silica gel 60 (0.063-0.200 mm, Merck). Thin-layer chromatography (TLC) was performed on SiliaPlate™ R10011B-323 (Silicycle) or Silica gel 60 F_{254} (Merck). ^{1}H, ^{13}C and 2D NMR spectroscopic data were recorded on 300 MHz or 500 MHz Bruker FTNMR Ultra Shield spectrometers. ^{1}H NMR spectra are reported in ppm on the δ scale and referenced to the internal tetramethylsilane. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant(s) in Hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Perkin Elmer 783 FTS165 FT-IR spectrometer. High-resolution mass spectra were obtained on a liquid chromatograph-mass spectrometer (2690, LCT, Waters, Micromass). The optical rotations were recorded on a JASCO P-1020 polarimeter. Melting points were measured using an Electrothermal 9100 melting point apparatus and are uncorrected. Enantiopurity was determined using HPLC on an Agilent series 1200 equipped with a diode array UV detector using either CHIRALCEL® OD-H column (15 cm) or CHIRALPAK® AS-H column (15 cm) and a guard column (1 cm).

2. Experimentals and Characterization Data

2.1 General procedure for Horner-Wadsworth-Emmons olefination

To a solution of triethylphosphonoacetate (1.5 equiv) in THF (0.8 M) at 0 °C was added NaH (60% in mineral oil, 2.5 equiv). The mixture was stirred at this temperature for 0.5 h and was added a solution of aldehyde derivative (1.0 equiv) in THF (0.8 M). The suspension was stirred from 0 °C to room temperature overnight. H_2O was then added and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the desired α,β-unsaturated ester derivative.

2.2 General procedure for hydrogenation

To a solution of α,β-unsaturated ester (1.0 equiv) in EtOAc (0.2 M) was added Pd/C (5 wt.%, 10 mol%). The reaction mixture was stirred at rt under H_2 atmosphere. After completion of reaction, it was filtered through a pad of Celite, washed with EtOAc and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the ester derivative.

2.3 General procedure for $LiAlH_4$ reduction

To a stirred suspension of $LiAlH_4$ (1.5 equiv) in THF (0.4 M) was added dropwise a solution of ester derivative (1.0 equiv) in THF (0.3 M) at 0 °C. The reaction mixture was stirred under argon from 0 °C to rt for 1 h. The reaction mixture was then added H_2O, conc. HCl and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography gave the corresponding alcohol derivative.

2.4 General procedure for oxidation

To a stirred solution of 2-iodoxybenzoic acid (IBX) (1.7 equiv) in DMSO (0.3 M) was added a solution of alcohol derivative (1.0 equiv) in CH_2Cl_2 (0.2 M) at room temperature. After completion of the reaction, it was filtered (CH_2Cl_2 as an eluent), diluted with H_2O and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with H_2O (x2), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography gave the corresponding aldehyde derivative.

2.5 General procedure for allylation

To a solution of aldehyde derivative (1.0 equiv) in THF (0.5 M) was added allylMgBr (1.0 M in Et_2O, 1.5 equiv) at –78 °C. The reaction mixture was stirred from –78 °C to 0 °C over 4 h before saturated NH_4Cl was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic extracts were washed with brine (20 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the racemic homoallylic alcohol derivative.

2.6 General procedure for Keck allylation

To a stirred suspension of oven-dried 4 Å molecular sieves in CH_2Cl_2 were added (*S*)- or (*R*)-BINOL catalyst (0.2 equiv) and 1.0 M solution of Ti(O*i*-Pr)$_4$ in CH_2Cl_2 (0.1 equiv). The suspension became brownish red and TFA (0.005 equiv) was added. The reaction mixture was heated at reflux for 4 h and then allowed to cool to rt. A solution of aldehyde derivative (1.0 equiv) in CH_2Cl_2 (0.05 M) was then added and the mixture was stirred for 0.5 h at room temperature. The reaction mixture was then cooled to –78 °C and allyltributyltin (1.2 equiv) was slowly added, stirred at the same temperature for additional 20 min before being kept in a freezer (–20 °C). After complete consumption of starting aldehyde, the reaction mixture was filtered through Celite (CH_2Cl_2 as an eluent) into a flask that contained saturated aqueous $NaHCO_3$ solution and the resulting mixture was stirred for 1 h before the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *invacuo*. Purification of the crude residue by column chromatography afforded the enantioenrichedhomoallylic alcohol derivative.

2.7 General procedure for O_3ReOH-catalyzed Prins cyclization reaction

To a solution of homoallylic alcohol derivative (1.0 equiv) in CH_2Cl_2 (0.1 M) was added aldehyde derivative(1.2 equiv), followed by O_3ReOH (65-70 wt% in H_2O or 75-80 wt% in H_2O) dropwise. The reaction mixture was stirred at room temperature overnight before being concentrated *invacuo*. Purification of the crude residue by column chromatography gave the 4-hydroxytetrahydropyran derivative.

2.8 General procedure for $BF_3 \cdot OEt_2$-mediated Prins cyclization reaction

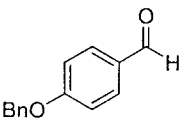
To a solution of homoallylic alcohol derivative (1.0 equiv) and aldehyde derivative (1 equiv) in dry CH_2Cl_2 (0.4 M) was added TMSOAc (5.0 equiv) and AcOH (7.0 equiv). The mixture was cooled to 0 °C and $BF_3 \cdot OEt_2$ (2.0 equiv) was added dropwise. The mixture was allowed to warm to rt and stirred under argon overnight. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *invacuo*. Purification of the crude residue by column chromatography gave the 4-acetoxytetrahydropyran product.

2.9 General procedure for methanolysis

To a solution of ester derivative (1.0 equiv) in MeOH (0.3 M) was added K_2CO_3 (1.5 equiv). The reaction mixture was stirred at rt for 1 h. H_2O was then added and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *invacuo*. Purification of the crude residue by column chromatography gave the corresponding alcohol product.

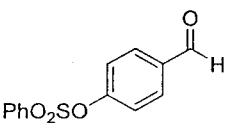
2.10 General procedure for Mitsunobu reaction

To a solution of alcohol derivative (1.0 equiv) in toluene (0.36 M) were added PPh_3 (4.4 equiv), 4-nitrobenzoic acid (4.8 equiv) and DIAD (4.2 equiv). The reaction mixture was stirred overnight before saturated aqueous $NaHCO_3$ was added and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *invacuo*. Purification of the crude residue by column chromatography furnished 4-nitrobenzoate ester derivative.



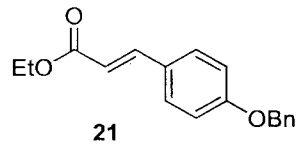
19

4-(Benzyloxy)benzaldehyde (19). To a solution of 4-hydroxybenzaldehyde (1.50 g, 12.3 mmol) in DMF (25 mL) was added K_2CO_3 (4.10 g, 29.5 mmol), followed by dropwise addition of benzyl bromide (1.80 mL, 14.7 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was then added 20 mL of H_2O and extracted with EtOAc (3x30 mL). The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) yielded **19** as a white solid (2.60 g, quant.):R_f = 0.83 (100% CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.80–7.33 (m, 5H), 7.08 (d, J = 8.7 Hz, 2H), 5.13 (s, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) δ190.7, 163.8, 136.1, 132.1, 130.2, 128.8, 128.4, 127.6, 115.2, 70.6. The spectral data of **19** matched those previously described.[1]



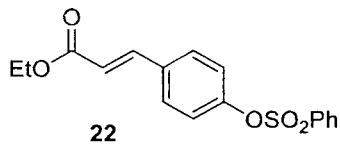
20

4-(Benzenesulfoxy)benzaldehyde (20). To a solution of 4-hydroxybenzaldehyde (3.07 g, 25.1 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added benzenesulfonyl chloride (4.80 mL, 36.8 mmol), followed by dropwise addition of Et_3N (10.0 mL, 73.7 mmol). The reaction mixture was stirred from 0 °C to rt overnight. The reaction mixture was then added 50 mL of H_2O and extracted with CH_2Cl_2 (3x40 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) yielded **20** as a white solid (6.55 g, quant.): R_f = 0.50 (10% EtOAc/hexanes); mp 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.91–7.78 (m, 4H), 7.71 (t, J = 7.5, Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 153.8, 135.1, 134.9, 134.7, 131.3, 129.4, 128.4, 123.6. The spectral data matched those previously reported.[2]



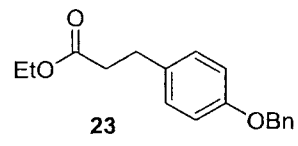
21

(*E*)-Ethyl 3-(4-(benzyloxy)phenyl)acrylate (21). (*E*)-Ethyl 3-(4-(benzyloxy)phenyl)acrylate (**21**) was prepared from benzaldehyde**19** (961.7 mg, 4.53 mmol) using the general procedure for Horner-Wadsworth-Emmons olefination. Purification by column chromatography (5% EtOAc/hexanes) gave **21** as a colorless oil (1.03 g, 81%): R_f = 0.52 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64(d, J = 15.9 Hz, 1H), 7.53–7.30 (m, 7H), 6.98 (d, J = 8.7 Hz, 2H), 6.31 (d, J = 15.9 Hz, 1H), 5.10 (s, 2H) 4.26 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). The spectral data matched those previously reported.[3]



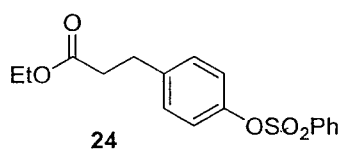
22

(*E*)-Ethyl 3-(4-(phenylsulfonyloxy)phenyl)acrylate (22). (*E*)-Ethyl 3-(4-(phenylsulfonyl-oxy)phenyl)acrylate (**22**) was prepared from benzaldehyde**20** (955.1 mg, 3.64 mmol) using the general procedure for Horner-Wadsworth-Emmons olefination. Purification by column chromatography (20% EtOAc/hexanes) gave **22** as a white solid (1.15 g, 95%): R_f = 0.29 (20% EtOAc/hexanes); mp 72–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0, 1.0 Hz, 2H), 7.70 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 16.0 Hz, 1H) 7.55 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 150.6, 142.8, 135.2, 134.4, 133.5, 129.3, 129.2, 128.5, 122.9, 119.4, 60.7, 14.3; IR (thin film) 3069, 2983, 1711, 1639, 1502, 1375 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{17}H_{16}NaO_5S$ (M + Na)$^+$ 355.0616, found 355.0615.



23

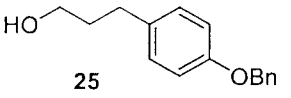
Ethyl 3-(4-(benzyloxy)phenyl)propanoate (23). Ethyl 3-(4-(benzyloxy)phenyl)propanoate (**23**) was prepared from α,β-unsaturated ester **21** (1.19 g, 4.3 mmol) using the general procedure for hydrogenation. Purification by column chromatography (20% EtOAc/hexanes) gave **23** as a colorless oil (1.08 g, 88%): R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.29 (m, 5H), 7.14 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 5.06 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). The spectral data matched those previously reported.[4]



24

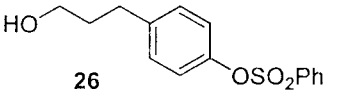
Ethyl 3-(4-(phenylsulfonyloxy)phenyl)propanoate (24). Ethyl 3-(4-(phenylsulfonyl-oxy)phenyl)propanoate (**24**) was prepared from α,β-unsaturated ester **22** (6.48 g, 19.5 mmol) using the general procedure for hydrogenation. Purification by column chromatography (10%

EtOAc/hexanes) gave **24** as a colorless oil (6.15 g, 94%): R_f = 0.31 (80% CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.1, 0.9 Hz, 2H), 7.58 (tt, J = 8.1, 0.9 Hz, 1H), 7.44 (td, J = 8.1, 0.9 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 4.01 (q, J = 7.2 Hz, 2H) 2.83 (t, J = 7.5 Hz, 2H), 2.50 (t, J = 7.5 Hz, 2H) 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 147.9, 139.8, 135.3, 134.4, 129.5, 129.2, 128.4, 122.2, 60.4, 35.5, 30.2, 14.2; IR (thin film) 2983, 1732, 1640, 1504, 1372, 1094 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{17}H_{18}NaO_5S$ $(M + Na)^+$ 357.0773, found 357.0772.



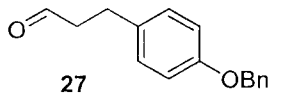
25

3-(4-(Benzyloxy)phenyl)propan-1-ol (25). 3-(4-(Benzyloxy)phenyl)propan-1-ol (**25**) was prepared from ester **23** (341.3 g, 1.2 mmol) using the general procedure for $LiAlH_4$ reduction. Purification by column chromatography (20% EtOAc/hexanes) gave **25** as a colorless oil (274.7 mg, 94%): R_f = 0.19 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.29 (m, 5H), 7.12 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 5.05 (s, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 1.87 (quintet, J = 6.5 Hz, 2H). The spectral data matched those previously described.[5]



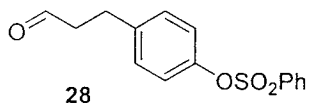
26

4-(3-Hydroxypropyl)phenylbenzenesulfonate (26). 4-(3-Hydroxypropyl)phenylbenzenesulfonate (**26**) was prepared from ester **24** (3.64 g, 10.9 mmol) using the general procedure for $LiAlH_4$ reduction. Purification by column chromatography (30% EtOAc/hexanes) gave **26** as a colorless oil (2.81 g, 88%): R_f = 0.21 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 2H), 7.64 (t, J = 7.5Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 3.59 (t, J = 6.3 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.79 (tt, J = 7.5, 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 141.2, 135.3, 134.3, 129.6, 129.2, 128.4, 122.1, 61.7, 33.9, 31.4; IR (thin film) 3377, 2940,1728, 1588, 1503, 1368 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{15}H_{16}NaO_5S$ $(M + Na)^+$ 315.0667, found 315.0667.



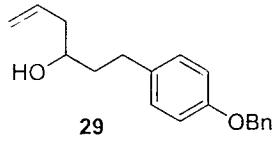
27

3-(4-(Benzyloxy)phenyl)propanal (27). 3-(4-(Benzyloxy)phenyl)propanal (**27**) was prepared from alcohol **25** (271.6 mg, 1.12 mmol) using the general procedure for oxidation. Purification by column chromatography (20% EtOAc/hexanes) gave **27** as a colorless oil (239.9 mg, 89%): R_f = 0.57 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.57–7.32 (m, 5H), 7.17 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 5.07 (s, 2H), 2.94 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 7.4 Hz, 2H).The spectral data matched those previously described.[6]



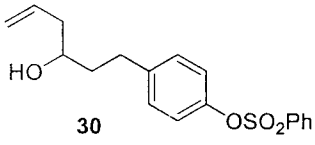
28

4-(3-Oxopropyl)phenylbenzenesulfonate (28). 4-(3-Oxopropyl)phenylbenzenesulfonate (**28**) was prepared from alcohol **26** (4.80 g, 16.4 mmol) using the general procedure for oxidation. Purification by column chromatography (20% EtOAc/hexanes) gave **28** as a colorless oil (4.32 g, 91%): R_f = 0.41 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, J = 1.2 Hz, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H) 7.52 (t, J = 7.5 Hz, 2H) 7.10 (d, J = 8.4 Hz, 2H) 6.89 (d, J = 8.4 Hz, 2H) 2.91 (t, J = 7.2 Hz, 2H) 2.75 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 148.0, 139.6, 135.5, 134.2, 129.5, 129.1, 128.5, 122.4, 45.0, 27.4. The spectral data matched those previously reported.[7]



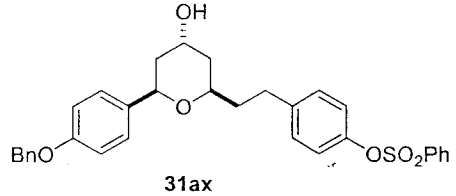
29

1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol (29). 1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol (**29**) was prepared from aldehyde **27** (235.4 mg, 0.98 mmol) using the general procedure for allylation. Purification by column chromatography (10% EtOAc/hexanes) gave **29** as a colorless oil (157.8 mg, 57%): R_f = 0.37 (20% EtOAc/hexanes); ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.51–7.28 (m, 5H), 7.13 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 5.94–5.73 (m, 1H), 5.24–5.11 (m, 2H), 5.05 (s, 2H), 3.78–3.61 (m, 1H), 2.87–2.56 (m, 2H), 2.41–2.11 (m, 2H), 1.87–1.72 (m, 2H).The spectral data matched those previously reported.[8]



30

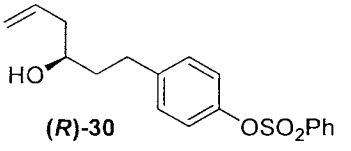
4-(3-Hydroxyhex-5-enyl)phenylbenzenesulfonate (30). 4-(3-Hydroxyhex-5-enyl)phenylbenzenesulfonate (**30**) was prepared from aldehyde **28** (1.05 g, 3.62 mmol) using the general procedure for allylation. Purification by column chromatography (80% CH_2Cl_2/hexanes) gave **30** as a colorless oil (782.6 mg, 65%): R_f = 0.63 (80% CH_2Cl_2/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.51 (t, J = 8.1 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.93–5.66 (m, 1H), 5.23–5.04 (m, 2H), 3.70–3.55 (m, 1H), 2.86–2.54 (m, 2H), 2.38–2.08 (m, 2H), 1.80–1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 141.3, 135.5, 134.4, 134.1, 129.5, 129.1, 128.5, 122.2, 118.5, 69.7, 42.0, 38.0, 31.8; IR (thin film) 3402, 2929, 1502, 1372, 1196, 1152 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{18}H_{20}NaO_4S$ $(M + Na)^+$ 355.0980, found 355.0980.



31ax

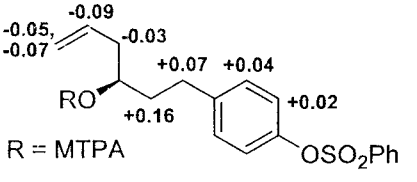
4-(2-((2*R*,4*R*,6*R*)-6-(4-(benzyloxy)phenyl)-4-hydroxytetrahydro-2*H*-pyran-2-yl)ethyl)-phenyl benzenesulfonate (31ax).Light yellow solid:R_f= 0.76 (5% EtOAc/CH_2Cl_2); mp 134–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J= 7.8 Hz, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.50

(t, J = 7.8 Hz, 2H), 7.47–7.27 (m, 7H), 7.08 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.06 (s, 2H), 4.76 (d, J = 11.5 Hz, 1H), 4.41–4.27 (m, 1H), 3.97–3.80 (m, 1H), 2.88–2.58 (m, 2H), 1.96–1.68 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 147.6, 141.5, 137.1, 135.6, 135.4, 134.1, 129.6, 129.1, 128.6, 128.5, 127.9, 127.4, 127.1, 122.1, 114.7, 73.0, 70.9, 70.1, 65.0, 40.4, 38.4, 37.6, 31.1; IR (thin film) 3430, 3034, 2921, 1513, 1373, 1178 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{32}H_{32}NaO_6S$ $(M + Na)^+$ 567.1817, found 567.1817.



(*R*)-30

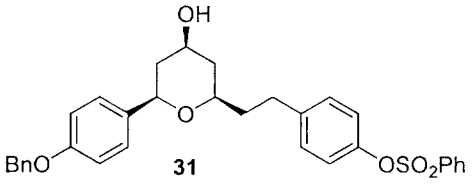
(*R*)-4-(3-Hydroxyhex-5-enyl)phenylbenzenesulfonate ((*R*)-30). (*R*)-4-(3-Hydroxyhex-5-enyl)phenylbenzenesulfonate (**(*R*)-30**) was prepared from aldehyde **28** (500.9 mg, 1.72 mmol) and (*S*)-BINOL using the general procedure for Keck allylation. Purification by column chromatography (80% CH_2Cl_2/hexanes) gave **(*R*)-30** as a colorless oil (434.6 mg, 76%, 98% ee): R_f = 0.63 (80% CH_2Cl_2/hexanes); $[??]_D^{25}$ = +12.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.89–5.71 (m, 1H), 5.20–5.04 (m, 2H), 3.70–3.56 (m, 1H), 2.84–2.56 (m, 2H), 2.36–2.21 (m, 2H), 1.83–1.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 141.4, 135.4, 134.6, 134.2, 129.6, 129.2, 128.5, 122.1, 118.2, 69.8, 42.0, 38.2, 31.3; IR (thin film) 3408, 2929, 1503, 1372, 1179, 1093 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{18}H_{20}NaO_4S$ $(M + Na)^+$ 355.0980, found 355.0980.The enantiomeric excess was determined on the corresponding acetate, which was prepared by acetylation with Ac_2O, from HPLC analysis using CHIRALCEL® OD-H column eluting with 2% isopropanol/hexane (flow rate = 0.6 mL/min, pressure = 18.6 bar, temp = 24-25 °C, λ = 254 nm): retention time = 19.57 min, retention time of (*S*)-enantiomer = 18.617 min. The absolute configuration was determined to be *R* by Mosher's method using the corresponding (*S*)-MTPA and (*R*)-MTPA esters.



MTPA ester of (*R*)-30

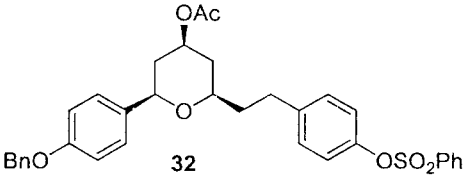
(*S*)-MTPA ester of (*R*)-30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 2H), 7.60–7.47 (m, 4H), 7.46–7.34 (m, 3H), 7.00 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.73–5.55 (m, 1H), 5.20–4.94 (m, 3H), 3.53 (s, 3H), 2.73–2.47 (m, 2H), 2.44–2.30 (m, 2H), 2.04–1.78 (m, 2H).

(*R*)-MTPA ester of (*R*)-30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.2 Hz, 2H), 7.66 (t, J = 7.2 Hz, 2H), 7.60–7.47 (m, 4H), 7.45–7.32 (m,3H), 6.94 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.84–5.59 (m, 1H), 5.29–4.99 (m, 3H), 3.55 (s, 3H), 2.65–2.31 (m, 4H), 1.99–1.75 (m, 2H).



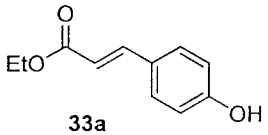
31

4-(2-((2*R*,4*S*,6*R*)-6-(4-(Benzyloxy)phenyl)-4-hydroxytetrahydro-2*H*-pyran-2-yl)ethyl) phenyl benzenesulfonate (31).Compound **31** was prepared from homoallylic alcohol(***R***)-**30**(107.3 mg, 0.32 mmol), aldehyde **19**(84.7 mg, 0.40 mmol) and O_3ReOH (75-80 wt%, 25 μL, 50 mol %). Purification of the crude residue by column chromatography (CH_2Cl_2 – 3% EtOAc/CH_2Cl_2)gave **31** as a light yellow oil (111.8 mg, 64%, 51% ee):R_f= 0.69 (5% EtOAc/CH_2Cl_2)[??]$_D^{24}$= +54.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.58–7.30 (m, 5H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.07 (d , *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.06 (s, 2H), 4.26 (d, *J* = 11.0 Hz, 1H), 4.00–3.80 (m, 1H), 3.49–3.30 (m, 1H), 2.80–2.56 (m, 2H), 2.17 (ddd, *J* = 12.3, 4.5, 1.5 Hz, 1H), 2.03–1.83 (m, 2H), 1.83–1.62 (m, 1H), 1.47 (q, *J* = 11.0 Hz, 1H), 1.28 (q, *J* = 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 147.7, 141.3, 137.1, 135.6, 134.6, 134.1, 129.6, 129.1, 128.6, 128.5, 128.0, 127.5, 127.2, 122.1, 114.8, 77.0, 74.7, 70.1, 68.5, 42.7, 40.9, 37.4, 31.1; IR (thin film) 3403, 3035, 2941, 1503, 1372, 1178 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{32}H_{32}NaO_6S$ (M + Na)$^+$ 567.1817, found 567.1818.The enantiomeric excess was determined on the corresponding acetate, which was prepared by acetylation with Ac_2O, from HPLC analysis using CHIRALCEL® OD-H column eluting with 20% isopropanol/hexane (flow rate = 1.0 mL/min, pressure = 36.7 bar, temp = 26-28 °C, λ = 270 nm): retention time = 14.539 min, retention time of (2*S*,4*R*,6*S*)-enantiomer = 18.63 min.



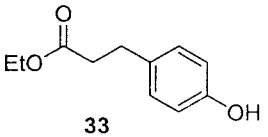
32

(2*R*,4*S*,6*R*)-2-(4-(Benzyloxy)phenyl)-6-(4-(phenylsulfonyloxy)phenethyl)tetrahydro-2*H*-pyran-4-yl acetate (32).Compound **32**was prepared from homoallylic alcohol **(*R*)-30** (60.1 mg, 0.18 mmol) and aldehyde **19** (39.4 mg, 0.18 mmol) using the general procedure for $BF_3{\cdot}OEt_2$-mediated Prins cyclization. Purification by column chromatography (10% EtOAc/hexanes) gave **32** as a colorless oil (38.2 mg, 48% based on 15.4 mg of recovered **(*R*)-30**,88% ee): R_f = 0.25 (20% EtOAc/hexanes); [??]$_D^{22}$ = +47.8 (*c* 0.23, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.48–7.27 (m, 5H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.13–4.97 (m, 1H), 5.09 (s, 2H), 4.45 (d, *J* = 10.5 Hz, 1H), 3.57–3.41 (m, 1H), 2.88–2.59 (m, 2H), 2.23 (ddd, *J* = 11.7, 4.8, 1.8 Hz, 1H), 2.11–1.86 (m, 2H), 2.06 (s, 3H), 1.85–1.71 (m, 1H), 1.59 (q, *J* = 11.7 Hz, 1H), 1.41 (q, *J* = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 158.3, 147.7, 141.1, 137.0, 135.5, 134.2, 134.1, 129.6, 129.1, 128.6, 128.5, 128.0, 127.4, 127.1, 122.2, 114.7, 76.8, 74.5, 70.6, 70.0, 38.9, 37.3, 37.1, 31.0, 29.7, 21.3; IR (thin film) 2929, 1739, 1503, 1375, 1242, 867 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{34}H_{34}NaO_7S$ (M + Na)$^+$ 609.1923, found 609.1916.The enantiomeric excess was determined by HPLC analysis using CHIRALCEL® OD-H column eluting with 20% isopropanol/hexane (flow rate = 1.0 mL/min, pressure = 36.7 bar, temp = 26-28 °C, λ = 270 nm): retention time = 14.546 min, retention time of (2*S*,4*R*,6*S*)-enantiomer = 18.68 min.



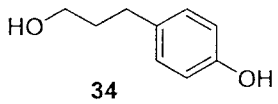
33a
E:Z = 69:21

Ethyl 3-(4-hydroxyphenyl)acrylate. To a solution of 4-hydroxybenzaldehyde (306.3 mg, 2.51 mmol) in CH_2Cl_2 (3 mL) and THF (2.5 mL) was added (carbethoxymethylene)-triphenylphosphorane (1.03 g, 3.08 mmol, 1.22 equiv).The reaction mixture was stirred at rt for 3 h. After the solvent was evaporated, the crude residue was purified by column chromato-graphy (20% EtOAc/hexanes) to furnish **33a** as a colorless oil (470.2 mg, 98%) as a 69:21 mixture of *E* and *Z* isomers: R_f = 0.36 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 0.67H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 15.9 Hz, 1H), 5.81 (d, *J* = 12.9 Hz, 0.32 H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.18 (d, *J* = 7.2 Hz, 0.69H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 167.6, 158.7, 157.4, 145.4, 144.1, 132.2, 130.1, 126.9, 126.5, 116.6, 116.0, 115.2, 114.7, 60.9, 60.7, 14.3, 14.1; IR (thin film) 3279, 2983, 1687, 1605, 1514, 1370 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{11}H_{12}NaO_3$ $(M + Na)^+$ 215.0684, found 215.0689.



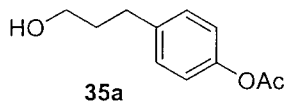
33

Ethyl 3-(4-hydroxyphenyl)propanoate (33). Ethyl 3-(4-hydroxyphenyl)propanoate (**33**) was prepared from α,β-unsaturated ester**33a** (4.55 g, 23.6 mmol) using the general procedure for hydrogenation. Purification by column chromatography (20% EtOAc/hexanes) yielded **33** as a colorless oil (4.53 g, 98%): R_f = 0.36 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 154.3, 132.2, 129.4, 115.4, 60.7, 36.4, 30.1, 14.2; IR (thin film) 2982, 1709, 1516, 1446, 1373, 1228 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{11}H_{14}NaO_3$ $(M + Na)^+$ 217.0841, found 217.0841.



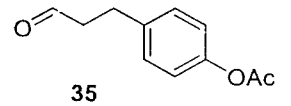
34

4-(3-Hydroxypropyl)phenol(34). 4-(3-Hydroxypropyl)phenol(**34**) was prepared from ester **33** (400 mg, 2.06 mmol) using the general procedure for $LiAlH_4$ reduction. Purification by column chromatography (30% EtOAc/hexanes) gave **34** as a colorless oil (300.4 mg, 95%): R_f = 0.27 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 3.68 (t, *J* = 6.6 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H),1.86 (tt, *J* = 7.2, 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 133.7, 129.5, 115.3, 62.3, 34.3, 31.1.The spectral data matched those previously reported.[9]



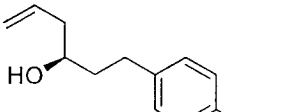
35a

4-(3-Hydroxypropyl)phenyl acetate (35a). To a solution of diol**34** (2.43 g, 16.0 mmol) in CH_2Cl_2 (20 mL) were added DMAP (590.3 mg, 4.79 mmol, 0.3 equiv) and Et_3N (1.2 mL, 7.98 mmol, 0.5 equiv). The mixture was cooled to 0 °C and acetic anhydride (750 μL, 7.98 mmol, 0.5 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 5 min before being quenched with 50 mL of H_2O and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated *invacuo*. Purification of the crude residue by column chromatography (20% EtOAc/hexanes) yielded **35a** as a colorless oil (1.86 g, 60%) along with bisacetylated product (650.7 mg, 17%): R_f = 0.57 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.61 (t, J = 6.6 Hz, 2H), 2.66 (t, J = 6.6 Hz, 2H), 2.26 (s, 3H), 1.84 (quintet, J = 6.6 Hz, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 148.7, 139.5, 129.4, 121.4, 61.9, 34.1, 31.4, 21.1; IR (thin film) 3342, 2939, 1755, 1508, 1371, 1219 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{11}H_{14}NaO_3$ $(M + Na)^+$ 217.0841, found 217.0841.



35

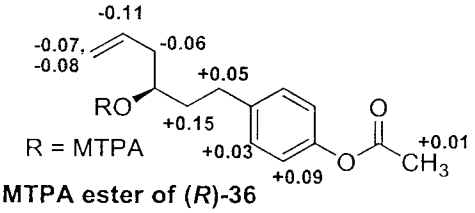
4-(3-Oxopropyl)phenyl acetate (35). 4-(3-Oxopropyl)phenyl acetate (**35**) was prepared from alcohol **35a** (510.6 mg, 2.63 mmol) using the general procedure for oxidation. Purification by column chromatography (20% EtOAc/hexanes) afforded **35** as a colorless oil (460.3 mg, 91%): R_f = 0.67 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 169.7, 149.1, 138.0, 129.3, 121.63, 121.56, 45.2, 27.4, 21.1; IR (thin film) 2933, 1761, 1723, 1509, 1370, 1219, 1197 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{11}H_{12}NaO_3$ $(M + Na)^+$ 215.0683, found 215.0683.



(*R*)-36

(*R*)-4-(3-Hydroxyhex-5-enyl)phenyl acetate ((*R*)-36). (*R*)-4-(3-Hydroxyhex-5-enyl)phenyl acetate (**(*R*)-36**) was prepared from aldehyde **35** (230 mg, 1.20 mmol) and (*S*)-BINOL using the general procedure for Keck allylation. Purification by column chromatography (80% CH_2Cl_2/hexanes) gave **(*R*)-36** as a colorless oil (150.8 mg, 54%, 96% ee): R_f = 0.27 (100% CH_2Cl_2); $[??]_D^{25}$ = +17.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 5.88–5.70 (m, 1H), 5.15–5.05 (m, 2H), 3.69–3.56 (m, 1H), 2.86–2.71(m, 1H), 2.70–2.56 (m, 1H), 2.33–2.09 (m, 2H), 2.25, (s, 3H), 1.78–1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 148.7, 139.7, 134.7, 129.4, 121.4, 118.1, 69.8, 42.1, 38.3, 31.4, 21.1; IR (thin film) 3074, 2931, 1762, 1508, 1370, 1196 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{14}H_{18}NaO_3$ $(M + Na)^+$ 257.1154, found 257.1155. The enantiomeric excess was determined by HPLC analysis using CHIRALPAK® AS-H column eluting with 10% isopropanol/hexane (flow rate = 0.5 mL/min, pressure = 17.8 bar, temp = 26-28 °C, λ = 263 nm): retention time = 11.203 min, retention time of (*S*)-enantiomer = 10.166 min. The

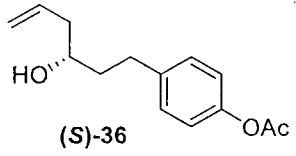
absolute configuration was determined to be *R* by Mosher's method using the corresponding (*S*)-MTPA and (*R*)-MTPA esters.



MTPA ester of (*R*)-36

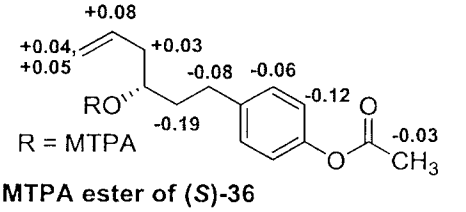
(*S*)-MTPA ester of (*R*)-36. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.34 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 5.84–5.52 (m, 1H), 5.37–5.12 (m, 1H), 5.10–5.00 (m, 2H), 3.58 (s, 3H), 2.84–2.52 (m, 2H), 2.50–2.35 (m, 2H), 2.29 (s, 3H), 2.13–1.82 (m, 2H).

(*R*)-MTPA ester of (*R*)-36. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.32 (m, 5H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.94–5.64 (m, 1H), 5.40–4.99 (m, 3H), 3.58 (s, 3H), 2.67–2.39 (m, 4H), 2.28 (s, 3H), 2.06–1.76 (m, 2H).



(*S*)-36

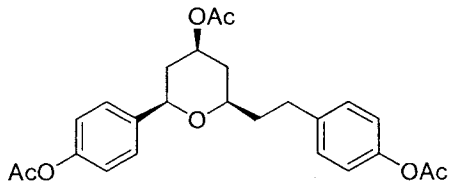
(*S*)-4-(3-Hydroxyhex-5-enyl)phenyl acetate ((*S*)-36). (*S*)-4-(3-Hydroxyhex-5-enyl)phenyl acetate ((*S*)-**36**) was prepared from aldehyde **35** (750.0 mg, 3.90 mmol) and (*R*)-BINOL using the general procedure for Keck allylation. Purification by column chromatography (80% CH_2Cl_2/hexanes) gave **(*S*)-36** as a colorless oil (402.4 mg, 44%, 96% ee): R_f = 0.27 (100% CH_2Cl_2); $[??]_D^{25}$ = –16.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 5.88–5.70 (m, 1H), 5.15–5.05 (m, 2H), 3.69–3.56 (m, 1H), 2.88–2.71 (m, 1H), 2.70–2.54 (m, 1H), 2.33–2.09 (m, 2H), 2.25, (s, 3H), 1.78–1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 148.7, 139.7, 134.7, 129.4, 121.4, 118.1, 69.9, 42.1, 38.3, 31.4, 21.1; IR (thin film) 3102, 2929, 1760, 1507, 1370, 1196, 1018 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{14}H_{18}NaO_3$ $(M + Na)^+$ 257.1154, found 257.1154. The enantiomeric excess was determined by HPLC analysis using CHIRALPAK® AS-H column eluting with 10% isopropanol/hexane (flow rate = 0.5 mL/min, pressure = 17.8 bar, temp = 26-28 °C, λ = 263 nm): retention time = 10.51 min, retention time of (*R*)-enantiomer = 12.023 min. The absolute configuration was determined to be *S* by Mosher's method using the corresponding (*S*)-MTPA and (*R*)-MTPA esters.



MTPA ester of (*S*)-36

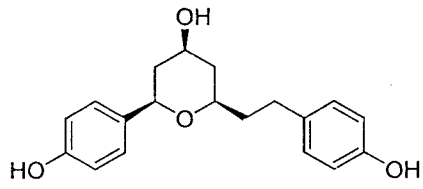
(*S*)-MTPA ester of (*S*)-36. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.32 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 5.90–5.57 (m, 1H), 5.34–4.92 (m, 3H), 3.55 (s, 3H), 2.67–2.36 (m, 4H), 2.26 (s, 3H), 2.02–1.77 (m, 2H).

(*R*)-MTPA ester of (*S*)-36. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.34 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 5.78–5.53 (m, 1H), 5.29–5.13 (m, 1H), 5.11–4.97 (m, 2H), 3.56 (s, 3H), 2.75–2.50 (m, 2H), 2.50–2.35 (m, 2H), 2.29 (s, 3H), 2.12–1.80 (m, 2H).



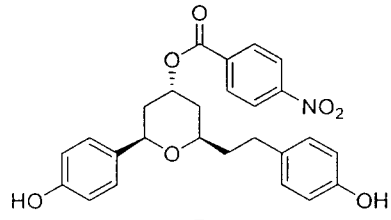
38

4-((2*R*,4*S*,6*R*)-4-Acetoxy-6-(4-acetoxyphenethyl)tetrahydro-2*H*-pyran-2-yl)phenyl acetate (38). Compound **38** was prepared from homolallylic alcohol **(*R*)-36** (110.8 mg, 0.47 mmol) and 4-acetoxybenzaldehyde (**37**) (78.2 mg, 0.47 mmol) using the general procedure for $BF_3{\cdot}OEt_2$-mediated Prins cyclization. Purification by column chromatography (10% EtOAc/hexanes) gave **38** as a colorless oil (110.9 mg, 53%, 85% ee):R_f = 0.37 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.19 (*J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.14–4.96 (m, 1H), 4.44 (dd, *J* = 11.7, 1.2 Hz, 1H), 3.64–3.48 (m, 1H), 2.88–2.68 (m, 2H), 2.42–2.21 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.12–1.90 (m, 2H), 2.06 (s, 3H), 1.90–1.72 (m, 1H), 1.56 (q, *J* = 11.7 Hz, 1H), 1.44 (q, *J* = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.6, 169.5, 150.0, 148.8, 139.5, 129.4, 126.9, 121.44, 121.39, 76.5, 74.6, 70.5, 39.1, 37.5, 37.0, 31.0, 21.3, 21.1; IR (thin film) 2929, 1732, 1508, 1369, 1239, 1196 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{25}H_{28}NaO_7$ $(M + Na)^+$ 463.1733, found 463.1733. The enantiomeric excess was determined by HPLC analysis using CHIRALCEL® OD-H column eluting with 15% isopropanol/hexane (flow rate = 0.8 mL/min, pressure = 28.3 bar, temp = 25-26 °C, λ = 263 nm): retention time = 13.722 min, retention time of (2*S*,4*R*,6*S*)-enantiomer = 11.416 min.



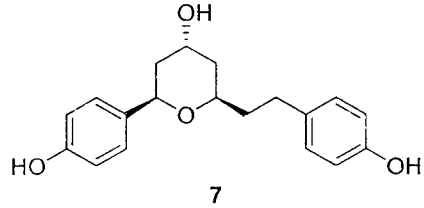
5

(1*R*,3*S*,5*R*)-1,7-bis(4-hydroxyphenyl)-1,5-epoxy-3-hydroxyheptane (5). Diarylheptanoid**5** was prepared from triacetate ester **38** (120.1 mg, 0.27 mmol) using the general procedure for methanolysis. Purification by column chromatography (40% EtOAc/hexanes) gave **5** as a white solid (74.3 mg, 88%): R_f = 0.37 (40% EtOAc/CH_2Cl_2);mp 186–188 °C; $[??]_D^{24}$ = +36.5 (*c* 0.22, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.23 (d, *J* = 11.7 Hz, 1H), 3.90–3.72 (m, 1H), 3.49–3.34 (m, 1H), 2.74–2.49 (m, 2H), 2.05 (ddd, *J* = 12.3, 4.2, 2.1 Hz, 1H), 1.94 (ddd, *J* = 12.3, 4.2, 2.1 Hz, 1H), 1.89–1.60 (m, 2H), 1.42 (q, *J* = 11.7 Hz, 1H), 1.21 (q, *J* = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 154.9, 153.4, 131.7, 131.4, 127.5, 125.7, 113.2, 113.1, 75.8, 73.5, 66.1, 40.6, 38.9, 36.3, 29.0; IR (thin film) 3174, 2945, 1702, 1516, 1367, 1236 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{19}H_{22}NaO_4$ $(M + Na)^+$ 337.1416, found 337.1416.



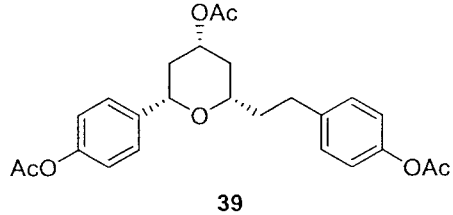
7a

(2*R*,4*R*,6*R*)-2-(4-Hydroxyphenethyl)-6-(4-hydroxyphenyl)tetrahydro-2*H*-pyran-4-yl 4-nitrobenzoate (7a). Ester 7awas prepared from tetrahydropyran**5** (42.3 mg, 0.13 mmol) using the general procedure for Mitsunobu reaction. Purification by column chromatography (20% EtOAc/hexanes) gave **7a** as a colorless oil (30.4 mg, 49%): R_f = 0.32 (40% EtOAc/hexanes); $[??]_D^{23}$ = +55.7 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.63–5.52 (m, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 3.99–3.83 (m, 1H), 2.82–2.61 (m, 2H), 2.17 (d, *J* = 13.2 Hz, 1H), 2.06–1.65 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 155.2, 153.7, 150.7, 135.8, 134.2, 133.9, 130.7, 129.5, 127.4, 123.7, 115.3, 115.2, 74.0, 72.0, 70.2, 37.6, 37.0, 35.2, 30.6; IR (thin film) 3019, 2925, 1722, 1515, 1347, 1277 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{26}H_{25}NaNO_7$ $(M + Na)^+$ 486.1529, found 486.1528.



7

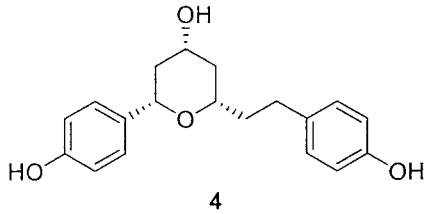
(1*R*,3*R*,5*R*)-1,7-bis(4-hydroxyphenyl)-1,5-epoxy-3-hydroxyheptane (7). Diarylheptanoid7was prepared from ester **7a** (24.6 mg, 0.053 mmol) using the general procedure for methanolysis. Purification by column chromatography (20% EtOAc/CH_2Cl_2) gave **7** as a white solid (14.8 mg, 89%): R_f = 0.47 (40% EtOAc/CH_2Cl_2);mp 186–188 °C; $[??]_D^{24}$ = +180.6 (*c* 0.02, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 7.5 Hz, 2H), 6.68 (d, *J* = 7.5 Hz, 2H), 4.70 (d, *J* = 10.5 Hz, 1H), 4.27–4.18 (m, 1H), 3.99–3.84 (m, 1H), 2.73–2.52 (m, 2H), 1.90–1.46 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 154.9, 153.4, 132.3, 131.5, 127.5, 125.7, 113.1, 113.0, 71.9, 69.7, 62.7, 37.9, 36.6, 36.3, 28.8; IR (thin film) 3399, 2921, 1698, 1597, 1515, 1243 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{19}H_{22}NaO_4$ $(M + Na)^+$ 337.1416, found 337.1426.



39

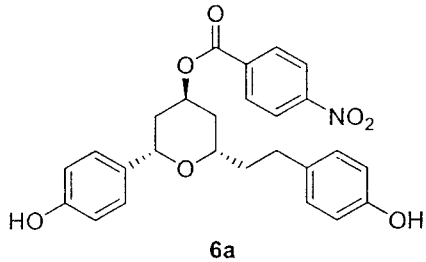
4-((2*S*,4*R*,6*S*)-4-Acetoxy-6-(4-acetoxyphenethyl)tetrahydro-2*H*-pyran-2-yl)phenyl acetate (39). Compound **39**was prepared from homoallylic alcohol **(*S*)-36** (300.1 mg, 1.28 mmol) and 4-acetoxybenzaldehyde (**37**) (218.6 mg, 1.28 mmol) using the general procedure for $BF_3{\cdot}OEt_2$-mediated Prins cyclization. Purification by column chromatography (10% EtOAc/hexanes) gave **39** as a colorless oil (248.6 mg, 44%): R_f = 0.37 (20% EtOAc/hexanes);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 5.10–4.94 (m, 1H), 4.41 (dd, J = 11.7, 1.2 Hz, 1H), 3.62–3.44 (m, 1H), 2.90–2.61 (m, 2H), 2.41–2.17 (m, 2H), 2.28 (s, 3H), 2.27 (s, 3H), 2.03 (s, 3H), 2.01–1.90 (m, 1H), 1.87–1.70 (m, 1H), 1.52 (q, J = 11.7 Hz, 1H), 1.41 (q, J = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.7, 169.5, 150.0, 148.8, 139.5, 129.4, 126.9, 121.5, 121.4, 76.5, 74.6, 70.5, 39.1, 37.5, 37.0, 31.0, 21.3, 21.1; IR (thin film) 2929, 1732, 1509, 1369, 1196 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{25}H_{28}NaO_7$ $(M + Na)^+$ 463.1733, found 463.1733. The enantiomeric excess was determined by HPLC analysis using CHIRALCEL® OD-H column eluting with 20% isopropanol/hexane (flow rate = 1.0 mL/min, pressure = 36.7 bar, temp = 25-27 °C, λ = 270 nm): retention time = 10.891 min, retention time of (2*R*,4*S*,6*R*)-enantiomer = 14.553 min.



4

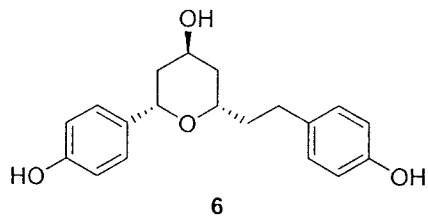
(1*S*,3*R*,5*S*)-1,7-bis(4-hydroxyphenyl)-1,5-epoxy-3-hydroxyheptane (4). Diarylheptanoid**4** was prepared from triacetate ester **39** (225.8 mg, 0.50 mmol) using the general procedure for methanolysis. Purification by column chromatography (40% EtOAc/hexanes) yielded **4** as a white solid (139.6 mg, 87%): R_f = 0.37 (40% EtOAc/CH_2Cl_2);mp 186–188 °C; $[??]_D^{24}$ = –35.2 (*c* 0.09, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.17 (d, J = 6.6 Hz, 2H), 6.96 (d, J = 6.6 Hz, 2H), 6.74 (d, J = 6.6 Hz, 2H), 6.66 (d, J = 6.6 Hz, 2H), 4.21 (d, J = 11.4 Hz, 1H), 3.87–3.70 (m, 1H), 3.47–3.33 (m, 1H), 2.71–2.49 (m, 2H), 2.04 (d, J = 12.0 Hz, 1H), 1.92 (d, J = 12.0 Hz, 1H), 1.87–1.75 (m, 1H), 1.75–1.59 (m, 1H), 1.41 (q, J = 11.1 Hz, 1H), 1.19 (q, J = 11.1 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 155.0, 153.4, 131.7, 131.4, 127.5, 125.7, 113.2, 113.1, 75.8, 73.5, 66.1, 40.6, 38.9, 36.3, 28.9; IR (thin film) 3176, 2945, 1701, 1516, 1235, 1067 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{19}H_{22}NaO_4$ $(M + Na)^+$ 337.1416, found 337.1416.



6a

(2*S*,4*S*,6*S*)-2-(4-Hydroxyphenethyl)-6-(4-hydroxyphenyl)tetrahydro-2*H*-pyran-4-yl 4-nitrobenzoate (6a). Ester **6a** was prepared from 4-hydroxytretahydropyran **4** (106.4 mg, 0.33 mmol) using the general procedure for Mitsunobu reaction. Purification by column chromatography (20% EtOAc/hexanes) gave **6a** as a colorless oil (63.7 mg, 41%): R_f = 0.32 (40% EtOAc/hexanes); $[??]_D^{23}$ = –55.3 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.64–5.41 (m, 1H), 4.74 (d, J = 11.4 Hz, 1H), 4.01–3.80 (m, 1H), 2.85–2.55 (m, 2H), 2.17 (d, J = 14.4 Hz, 1H), 2.11–1.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 155.2, 153.7, 150.7, 135.8, 134.2, 133.9, 130.7,

129.5, 127.4, 123.7, 115.3, 115.2, 74.0, 72.2, 70.2, 37.6, 37.0, 35.2, 30.6; IR (thin film) 3014, 2924, 1722, 1516, 1347, 1277, 1065 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{26}H_{25}NaNO_7$ $(M + Na)^+$ 486.1529, found 486.1530.

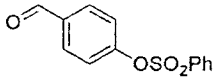


6

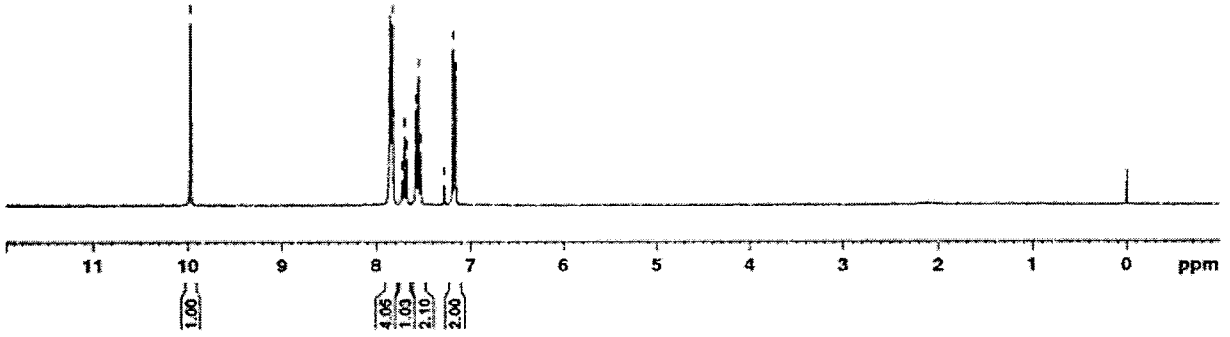
(1*S*,3*S*,5S)-1,7-bis(4-hydroxyphenyl)-1,5-epoxy-3-hydroxyheptane (6). Diarylheptanoid**6** was prepared from ester **6a** (30.2 mg, 0.065 mmol) using the general procedure for methanolysis. Purification by column chromatography (20% $EtOAc/CH_2Cl_2$) gave **6** as a white solid (17.6 mg, 86%): R_f = 0.47 (40% $EtOAc/CH_2Cl_2$); mp 186–188 °C; $[??]_D^{23}$ = –166.7 (*c* 0.01, MeOH); mp 186–188 °C; ^1H NMR (300 MHz, CD_3OD) δ 7.20 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.28–4.16 (m, 1H), 3.97–3.82 (m, 1H), 2.74–2.50 (m, 2H), 1.89–1.46 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 154.9, 153.4, 132.3, 131.5, 127.5, 125.7, 113.1, 113.0, 71.9, 69.7, 62.7, 37.9, 36.6, 36.3, 28.8; IR (thin film) 3137, 2922, 1702, 1613, 1516, 1239 cm^{-1}; HRMS (ESI) *m/z*calcd for $C_{19}H_{22}NaO_4$ $(M + Na)^+$ 337.1416, found 337.1413.

3. ^{1}H and ^{13}C NMR Spectra

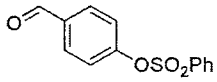
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of 4-formylphenyl benzenesulfonate (**20**)



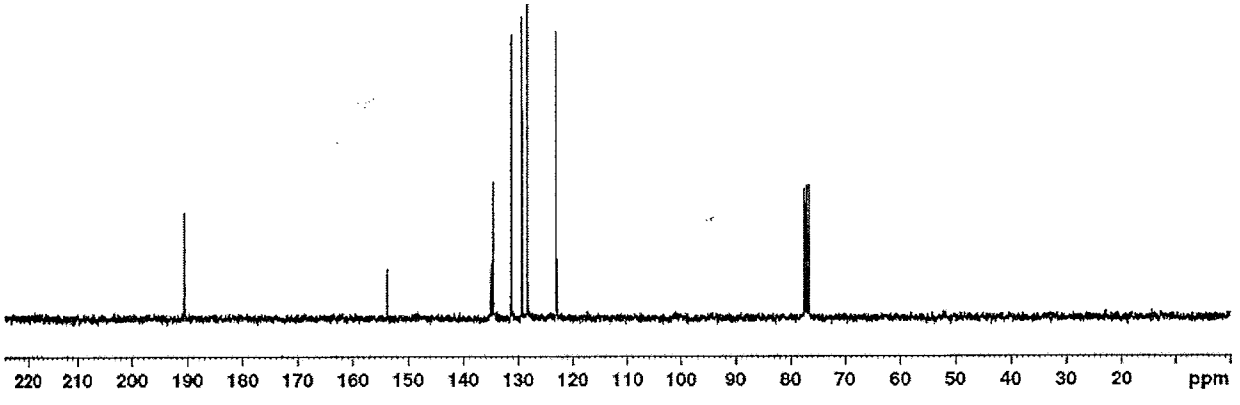
20



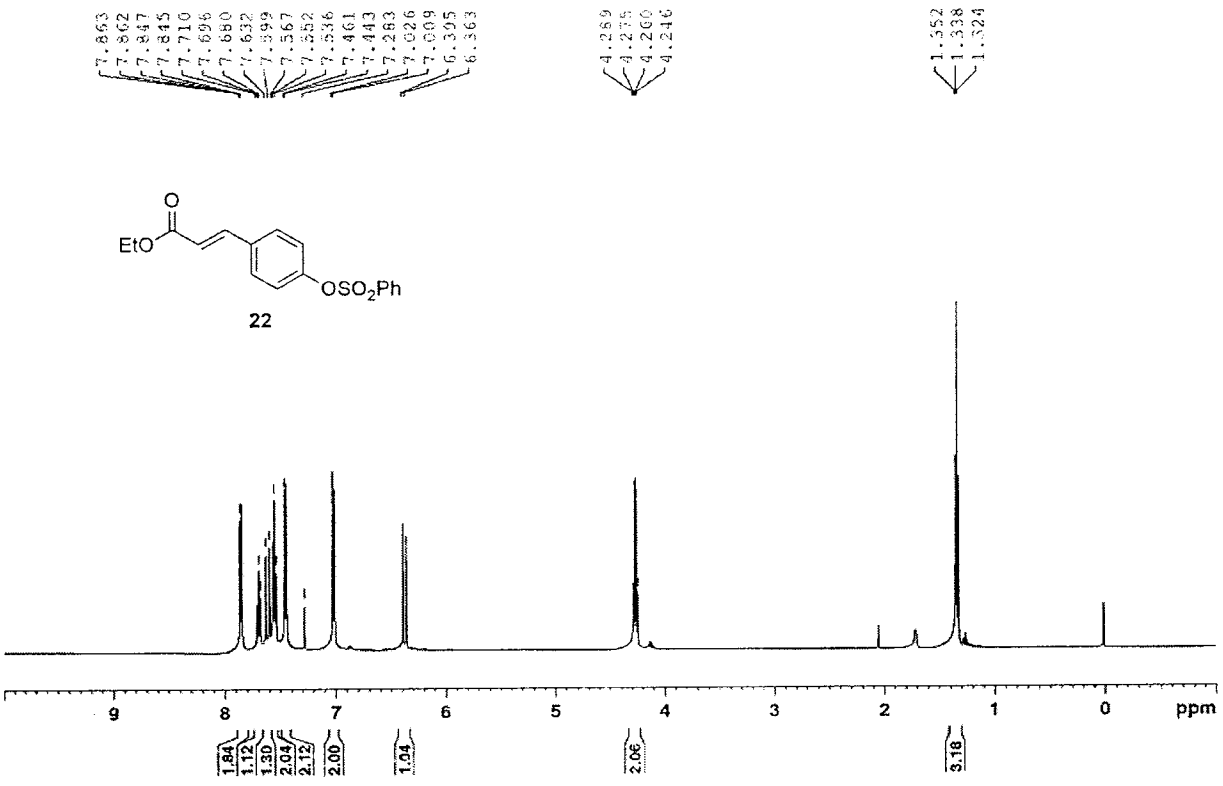
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of 4-formylphenyl benzenesulfonate (**20**)



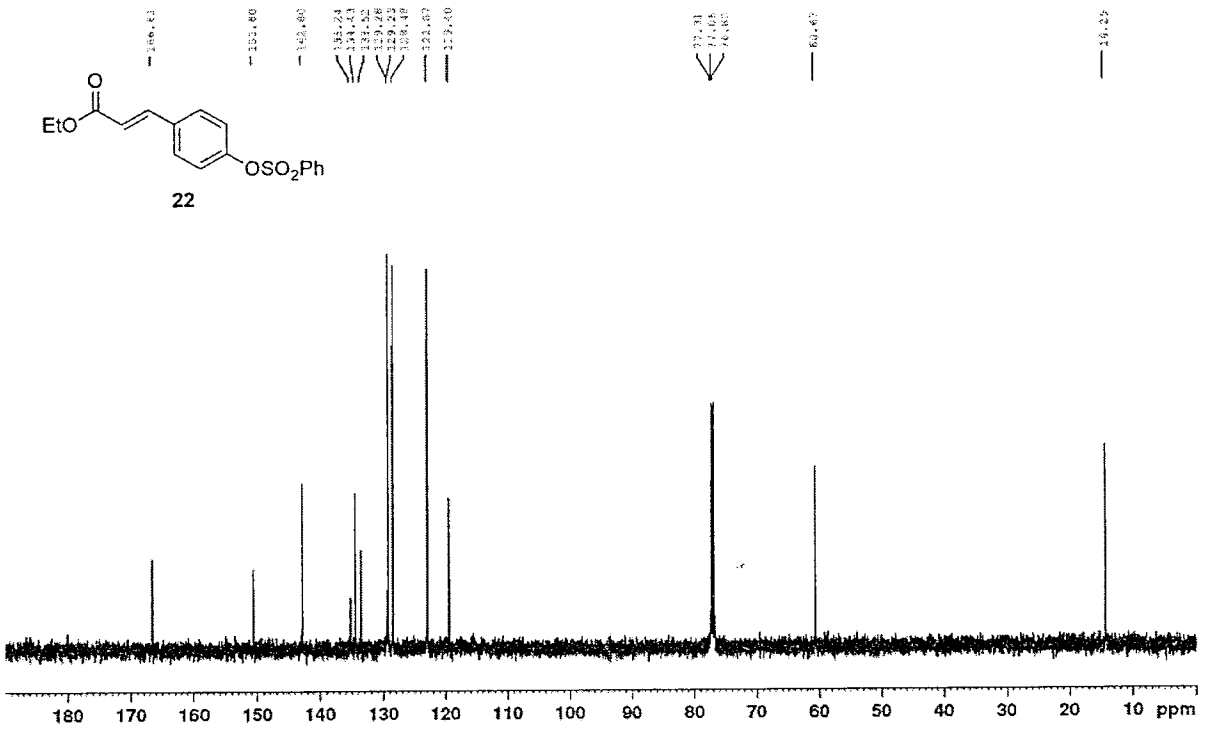
20



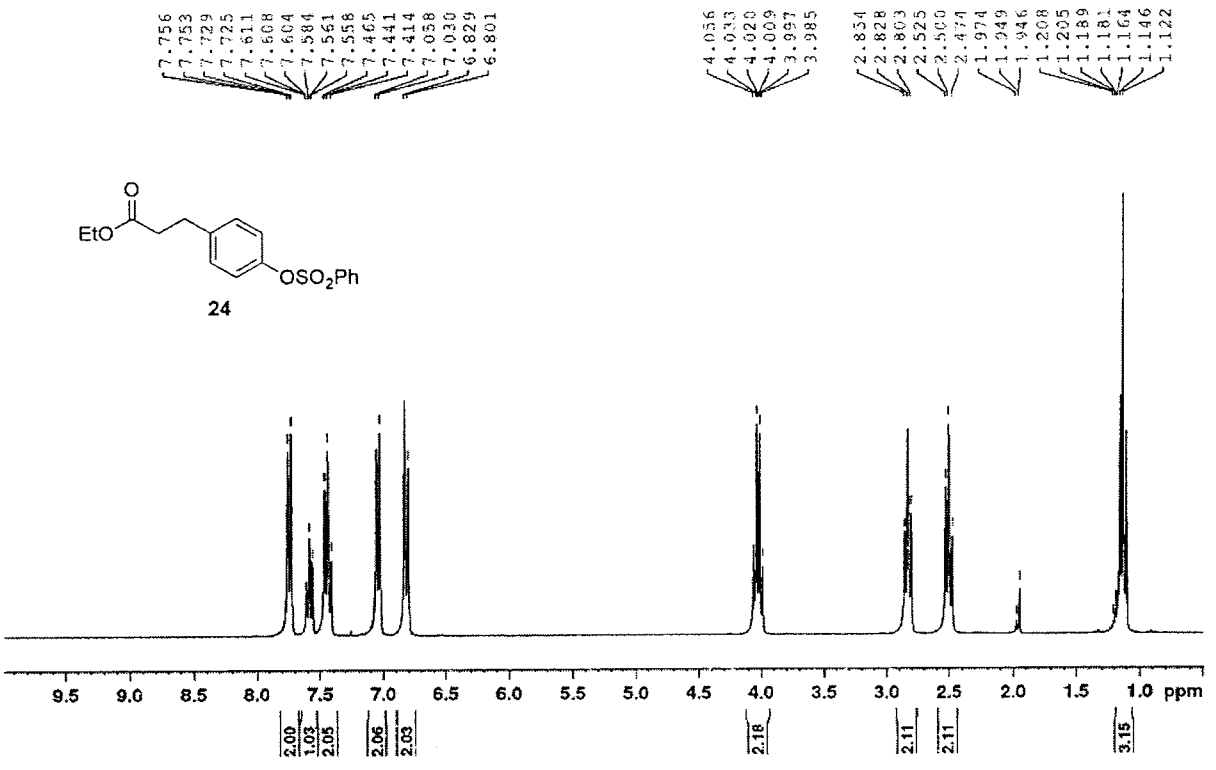
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*E*)-ethyl 3-(4-(phenylsulfonyloxy)phenyl)acrylate (**22**)



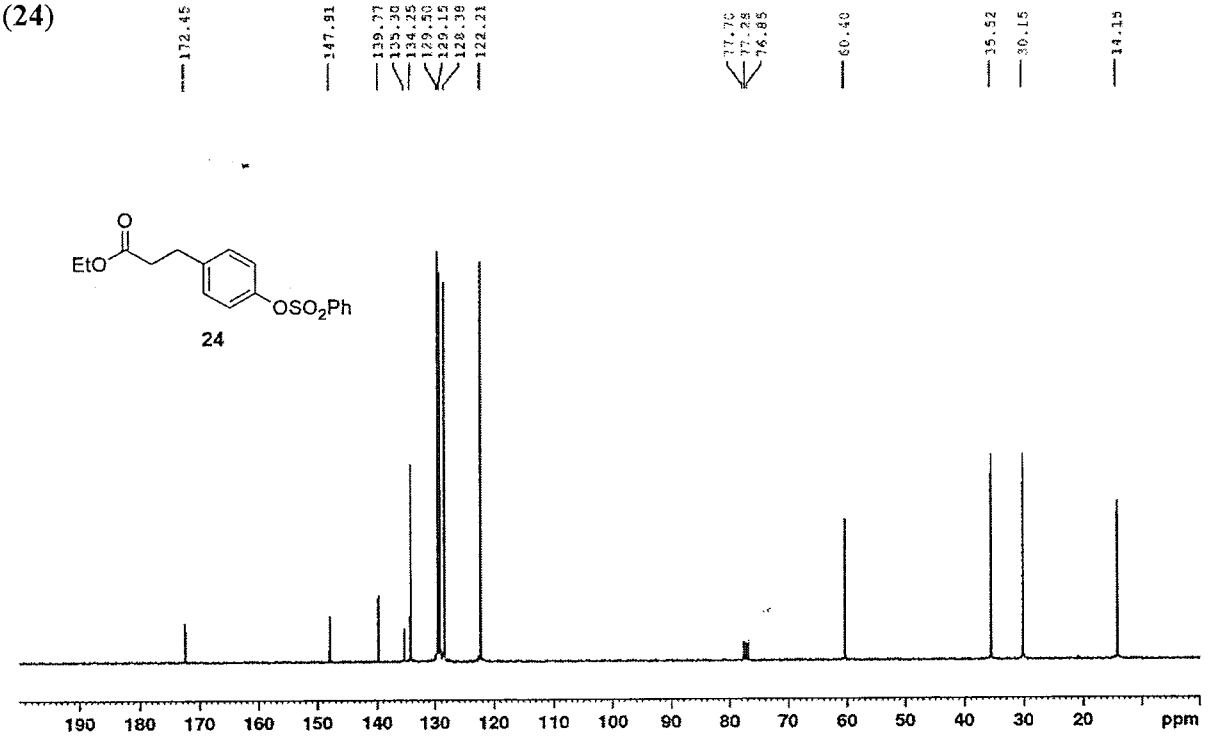
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of (*E*)-ethyl 3-(4-(phenylsulfonyloxy)phenyl)acrylate (**22**)



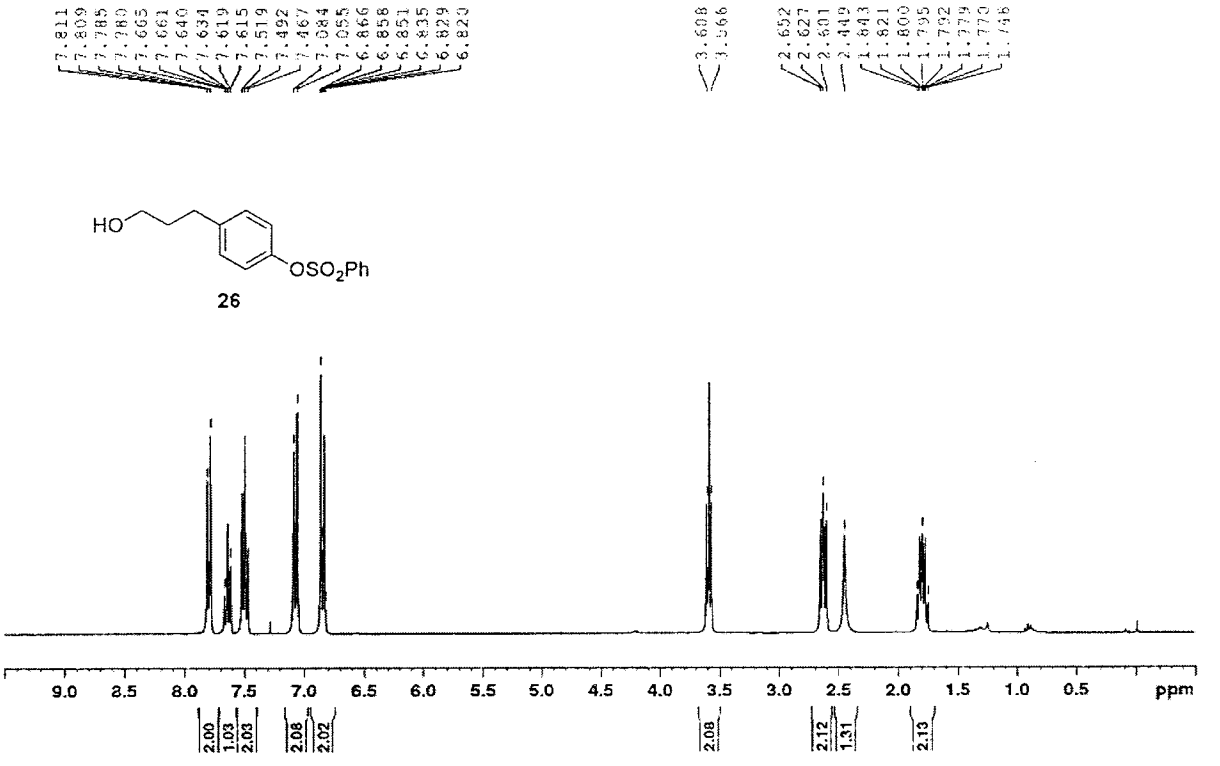
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ethyl 3-(4-(phenylsulfonyloxy)phenyl)propanoate (**24**)



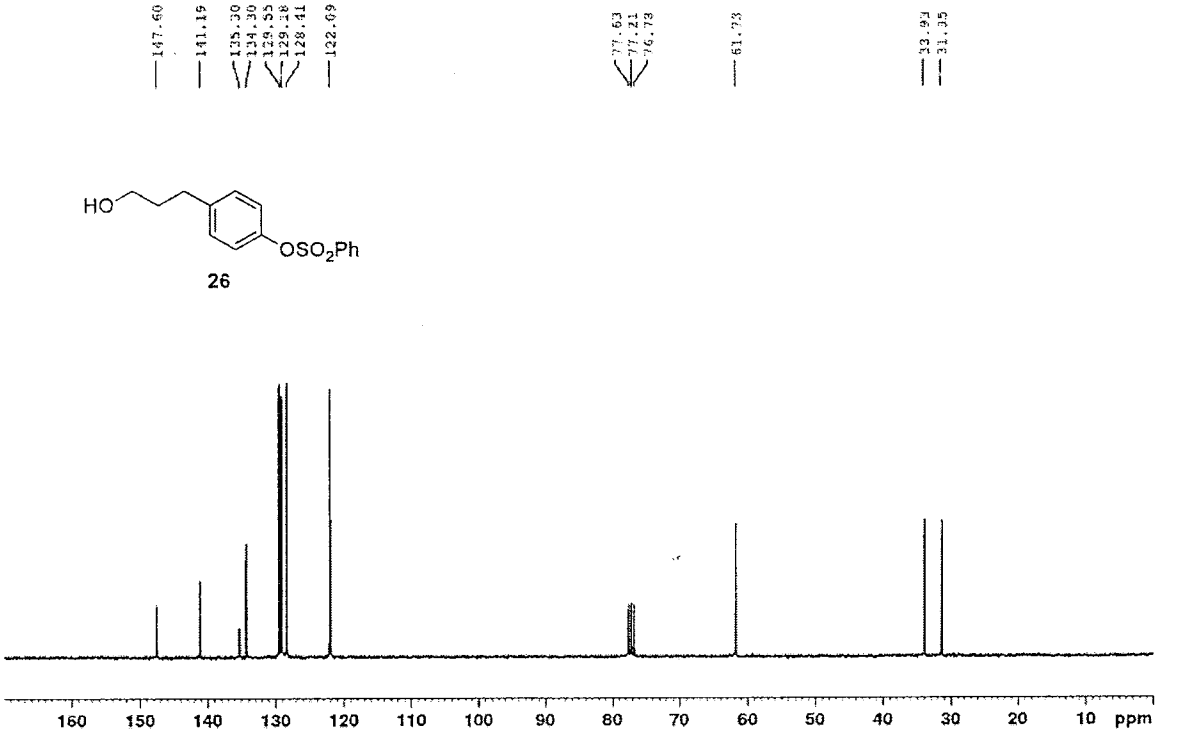
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ethyl 3-(4-(phenylsulfonyloxy)phenyl)propanoate (**24**)



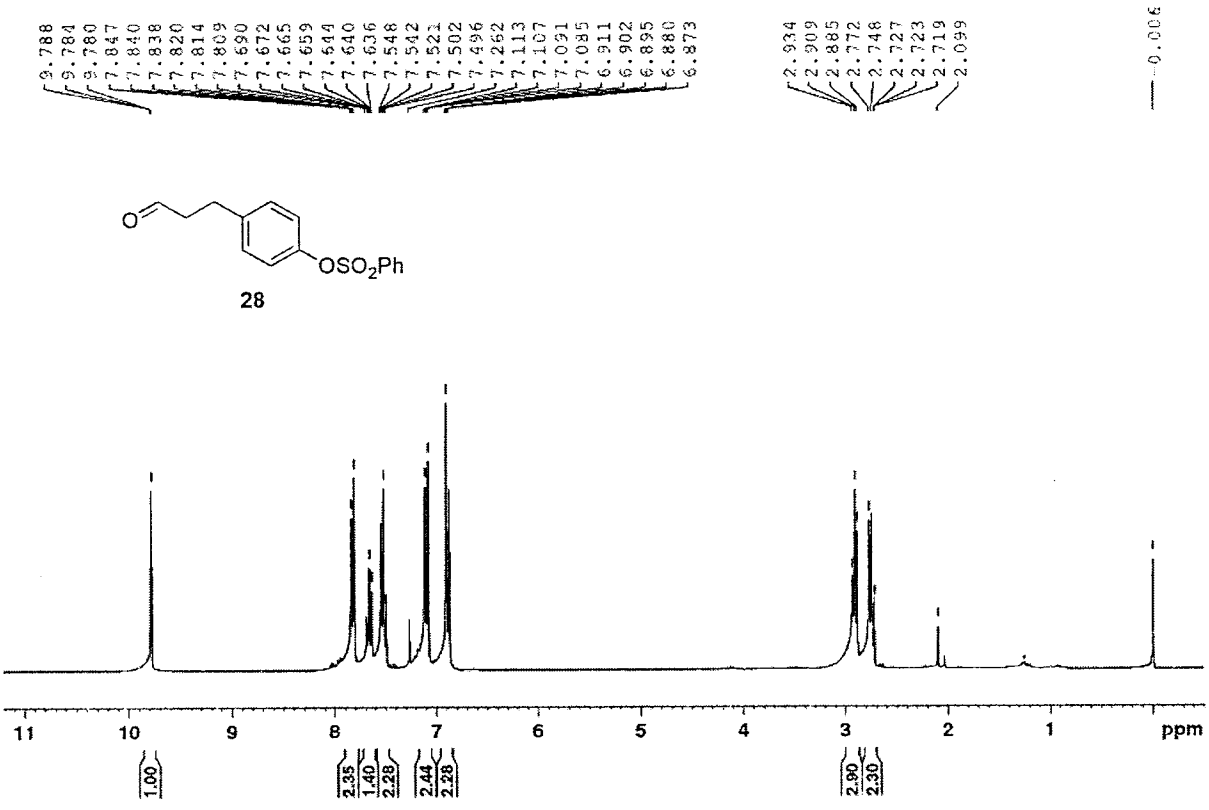
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of 4-(3-hydroxypropyl)phenylbenzenesulfonate (**26**)



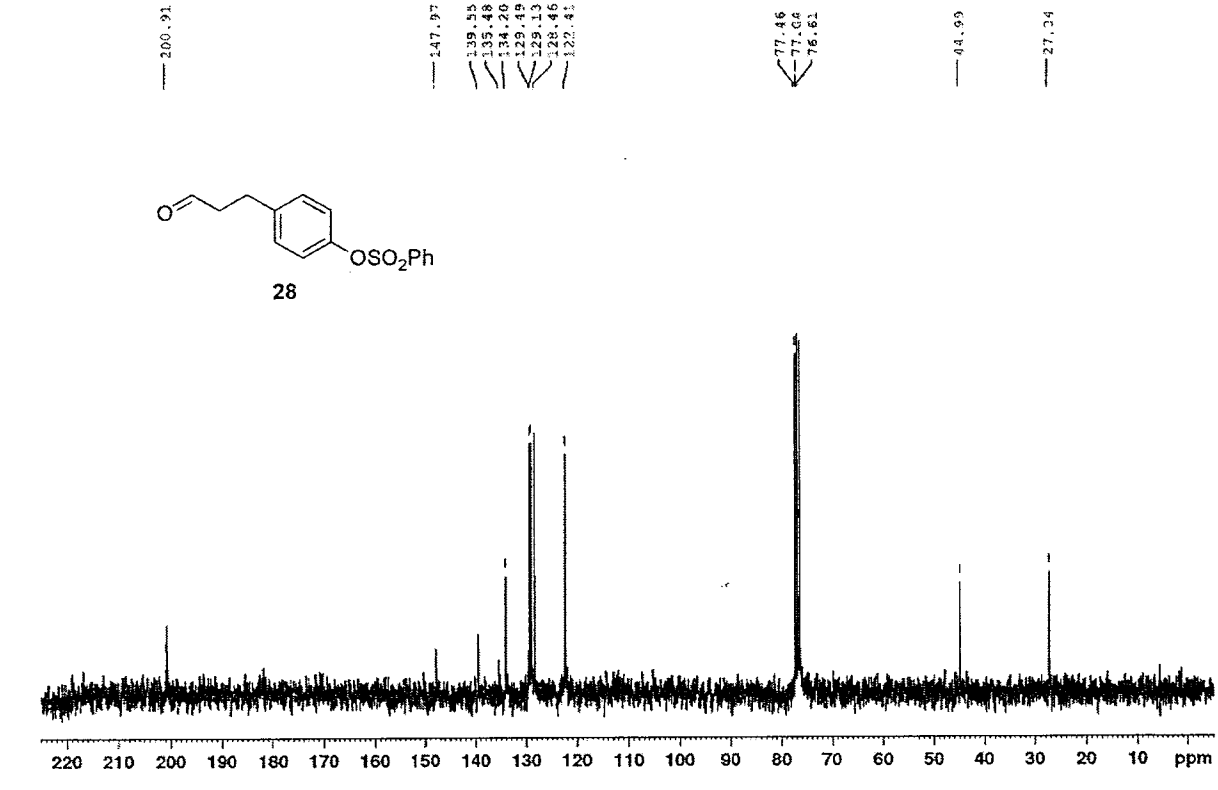
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of 4-(3-hydroxypropyl)phenylbenzenesulfonate (**26**)



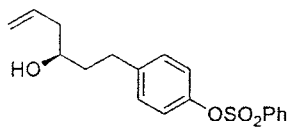
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of 4-(3-oxopropyl)phenylbenzenesulfonate (**28**)



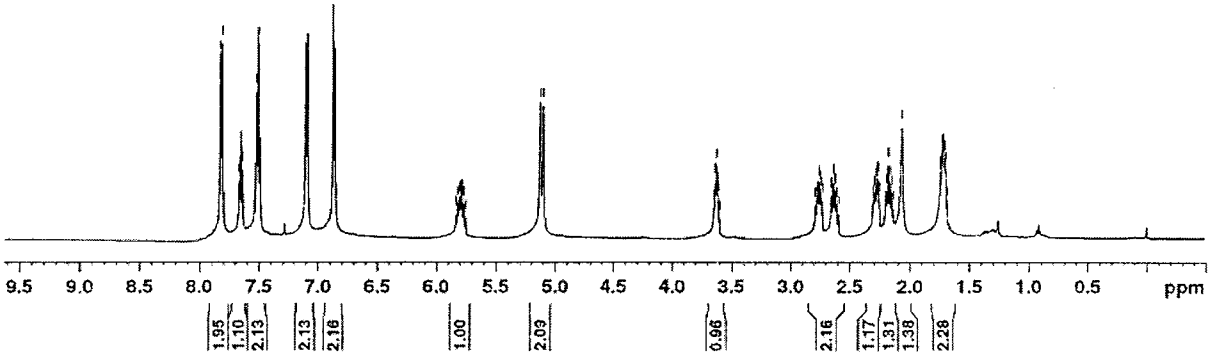
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of4-(3-oxopropyl)phenylbenzenesulfonate (**28**)



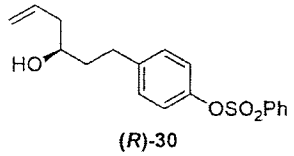
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **(*R*)-30**



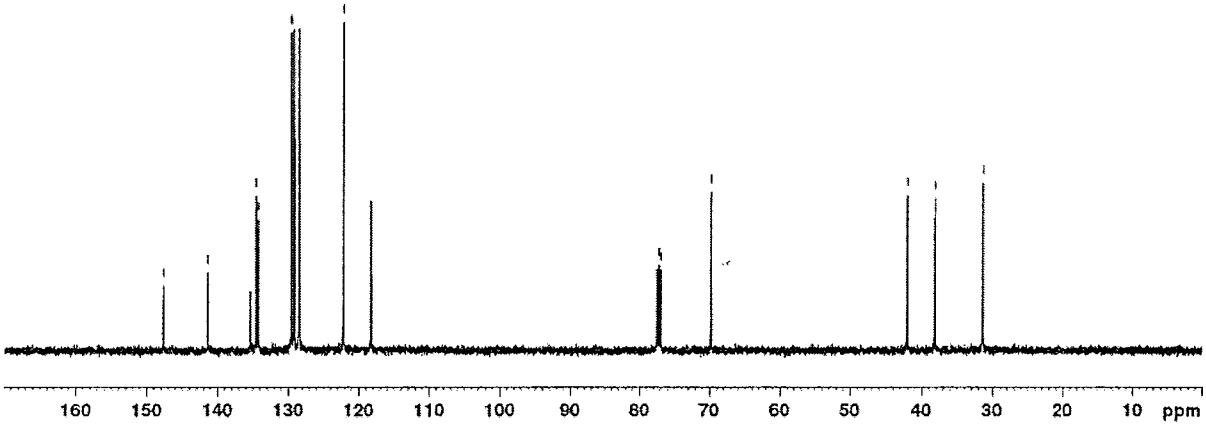
(*R*)-30



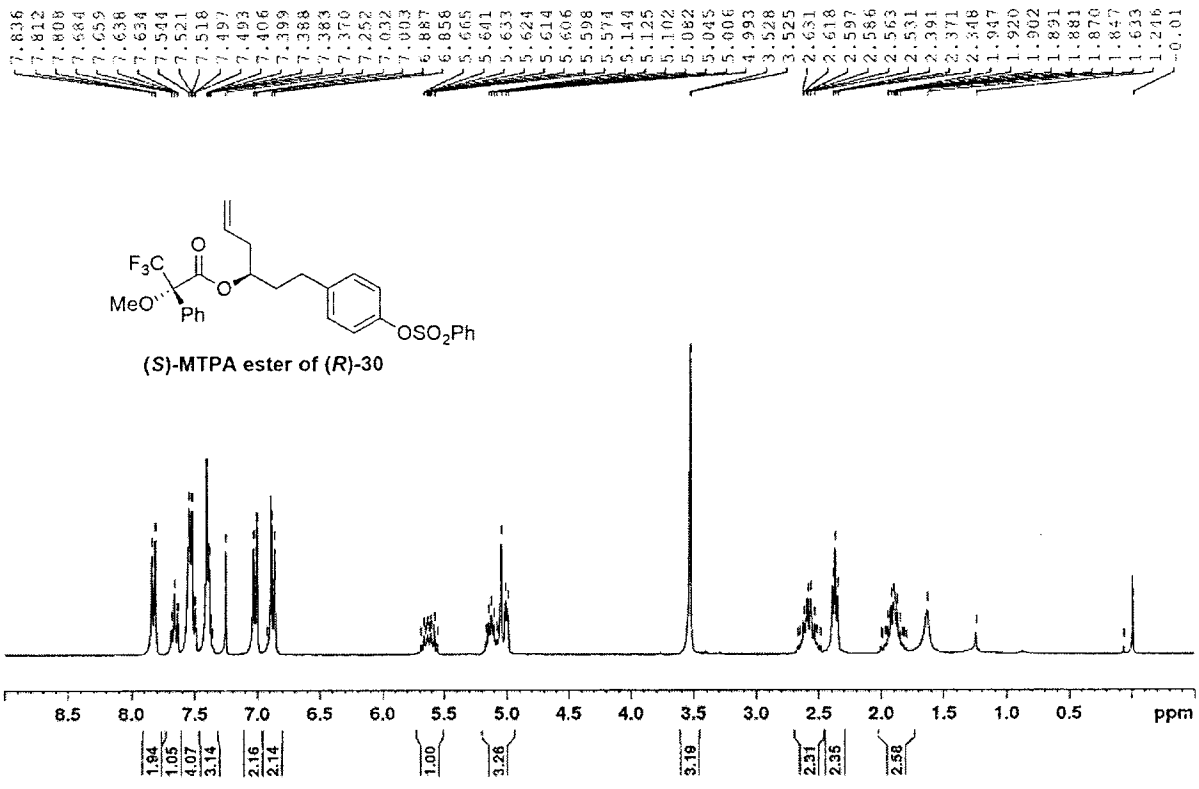
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **(*R*)-30**



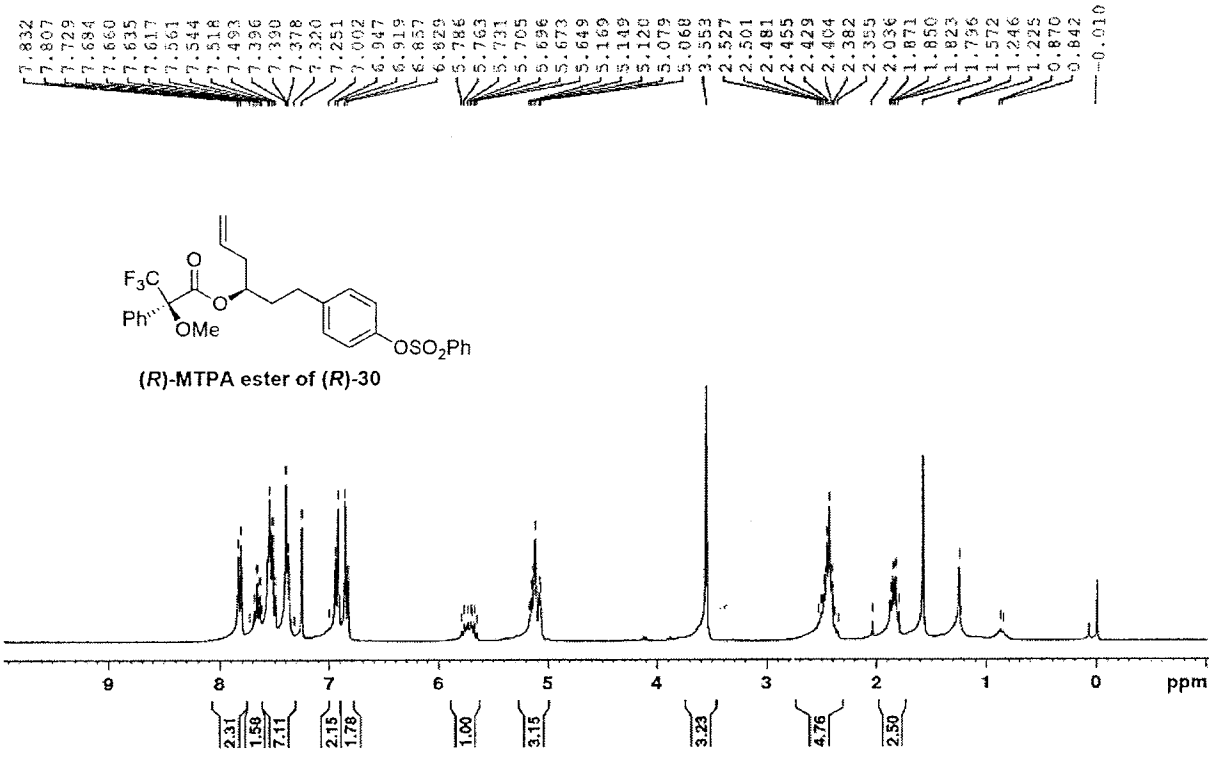
(*R*)-30



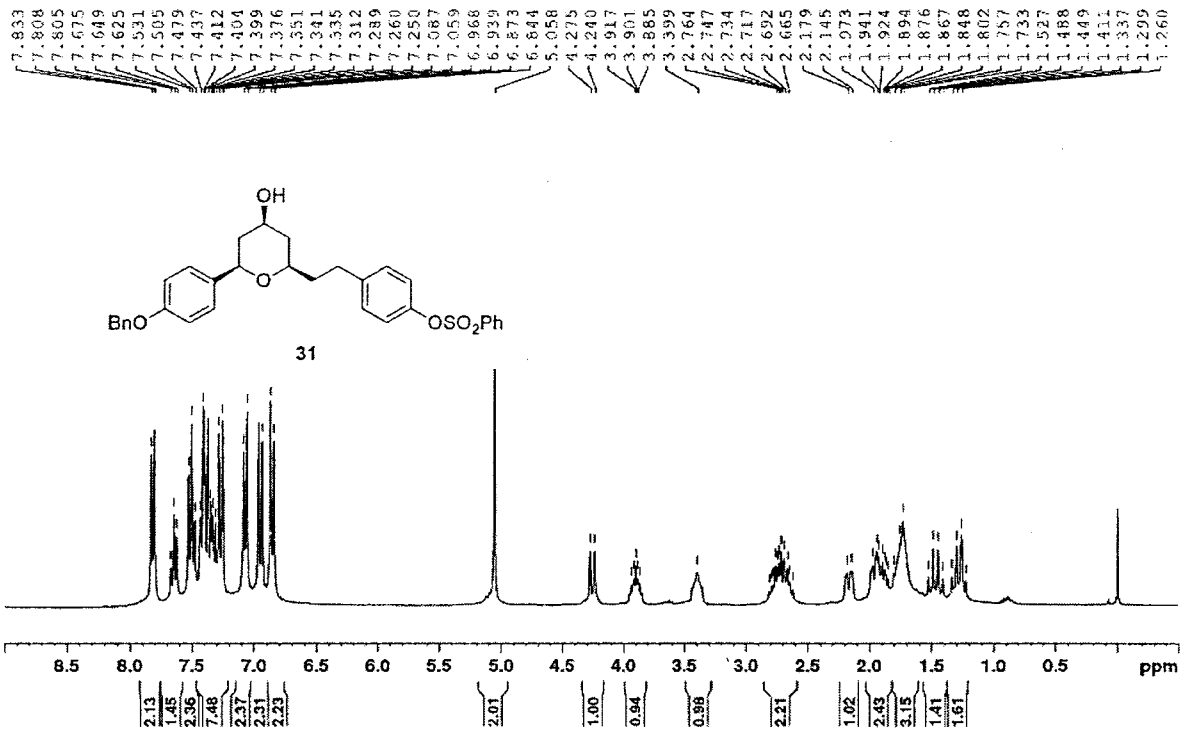
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*S*)-MTPA ester of **(*R*)-30**



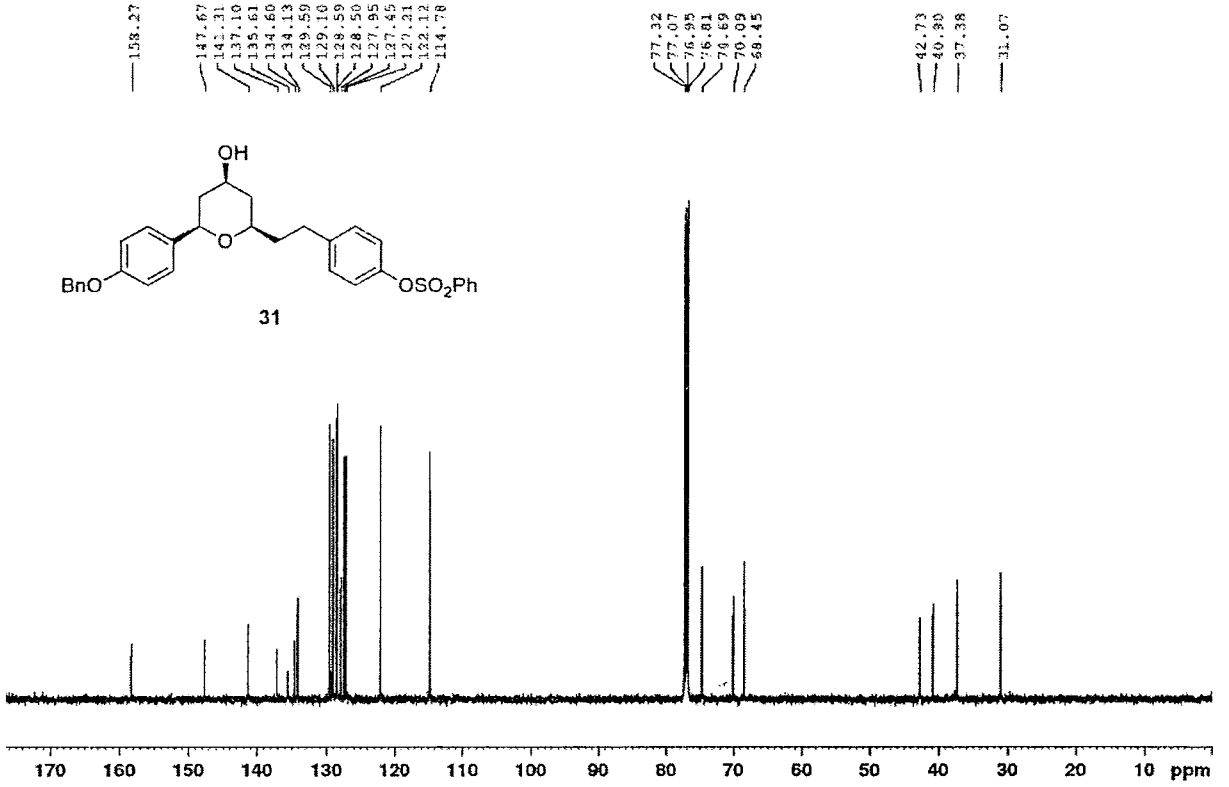
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*R*)-MTPA ester of **(*R*)-30**



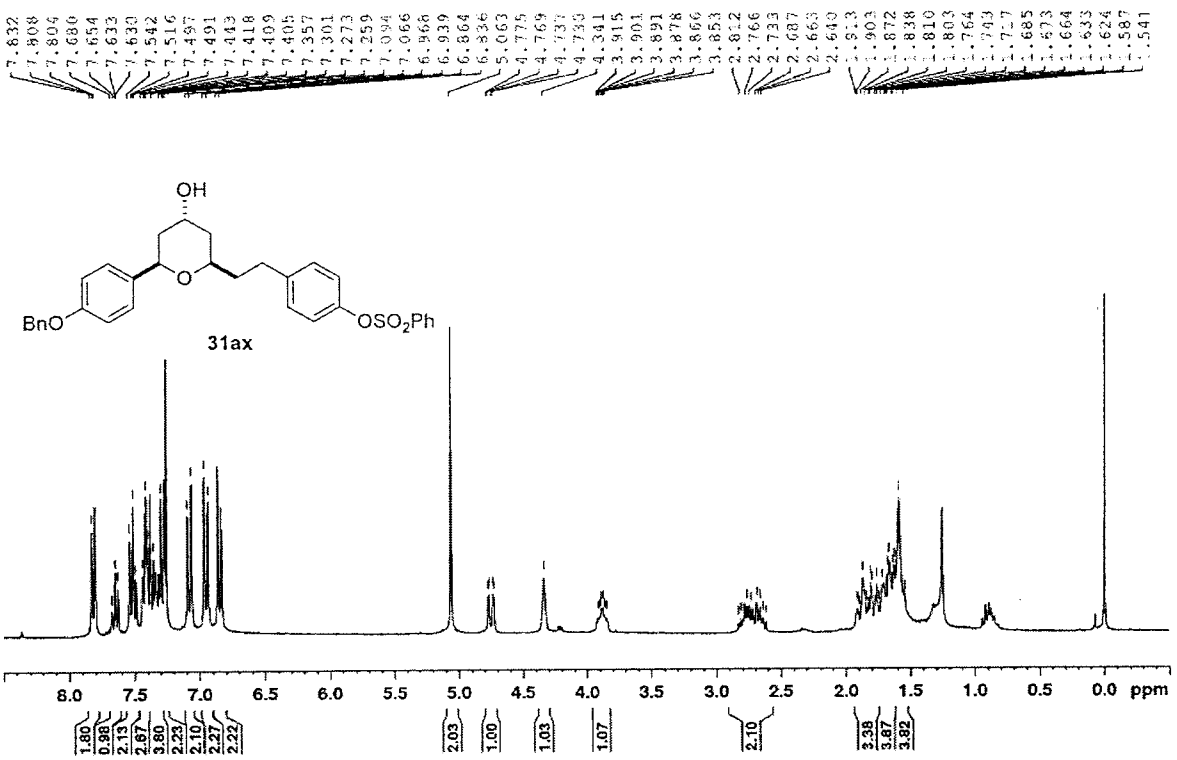
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **31**



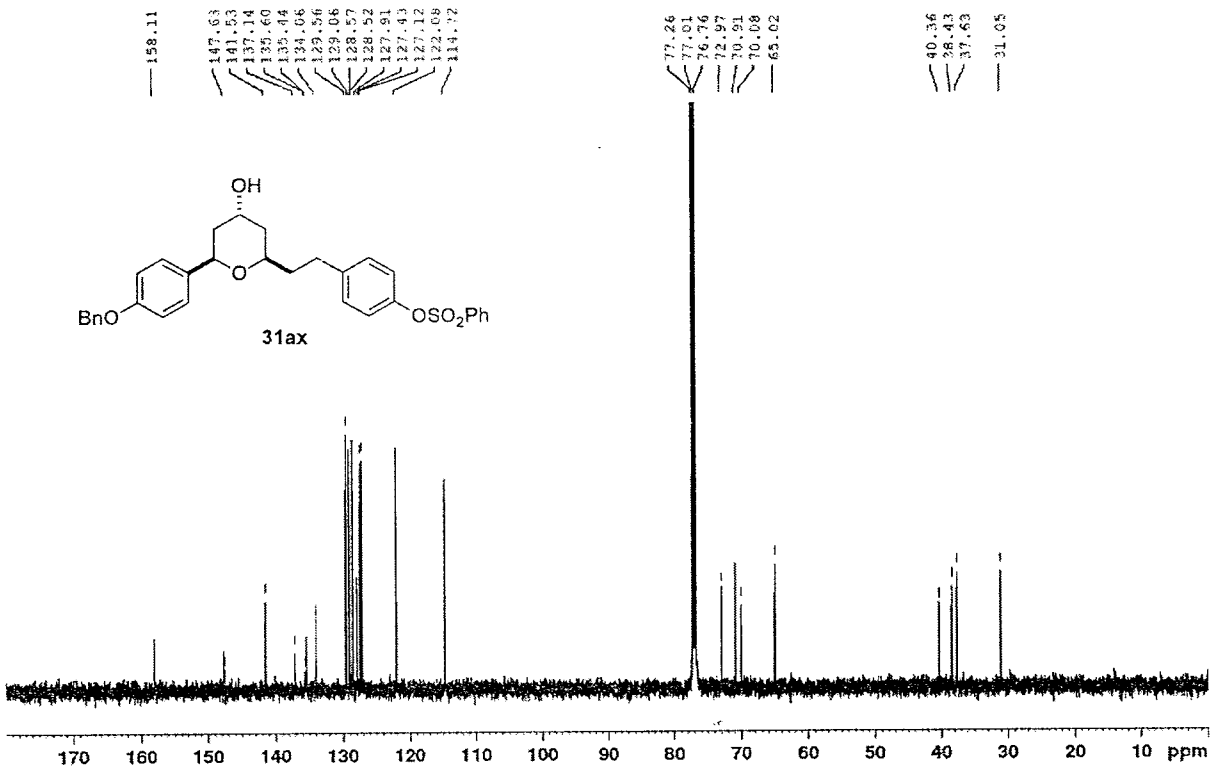
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **31**



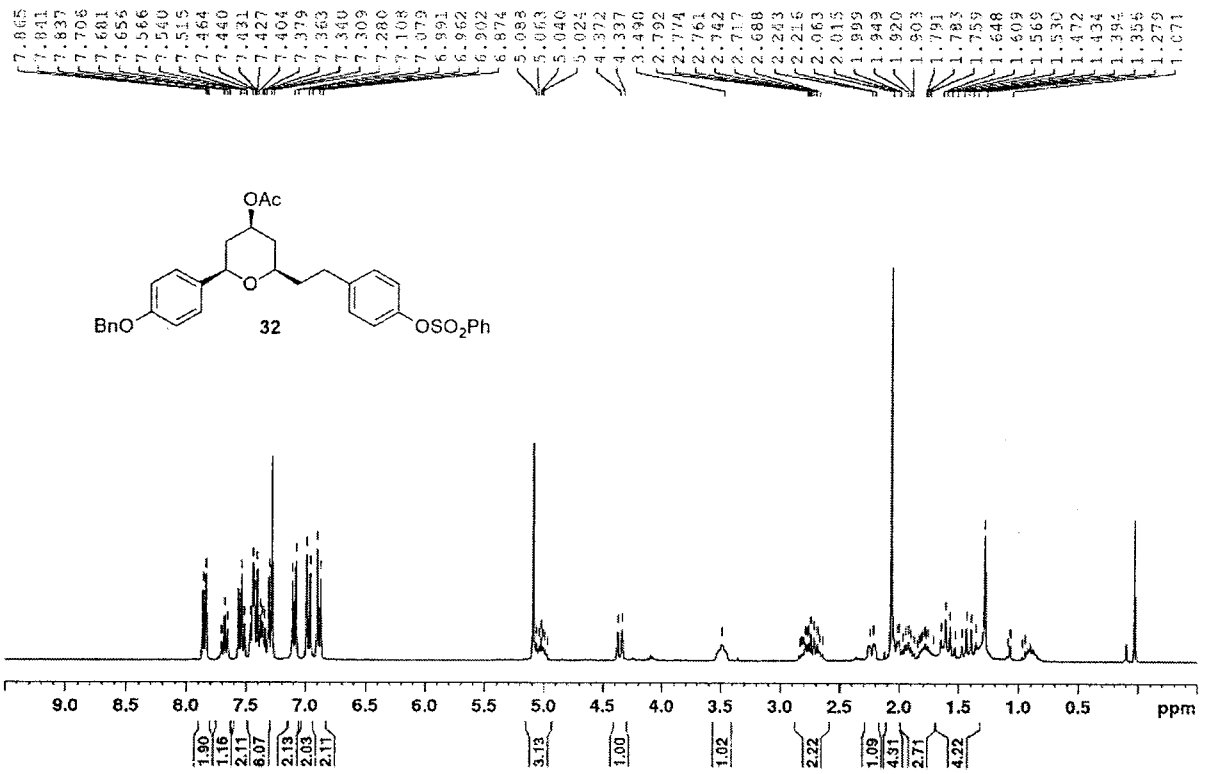
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of compound **31ax**



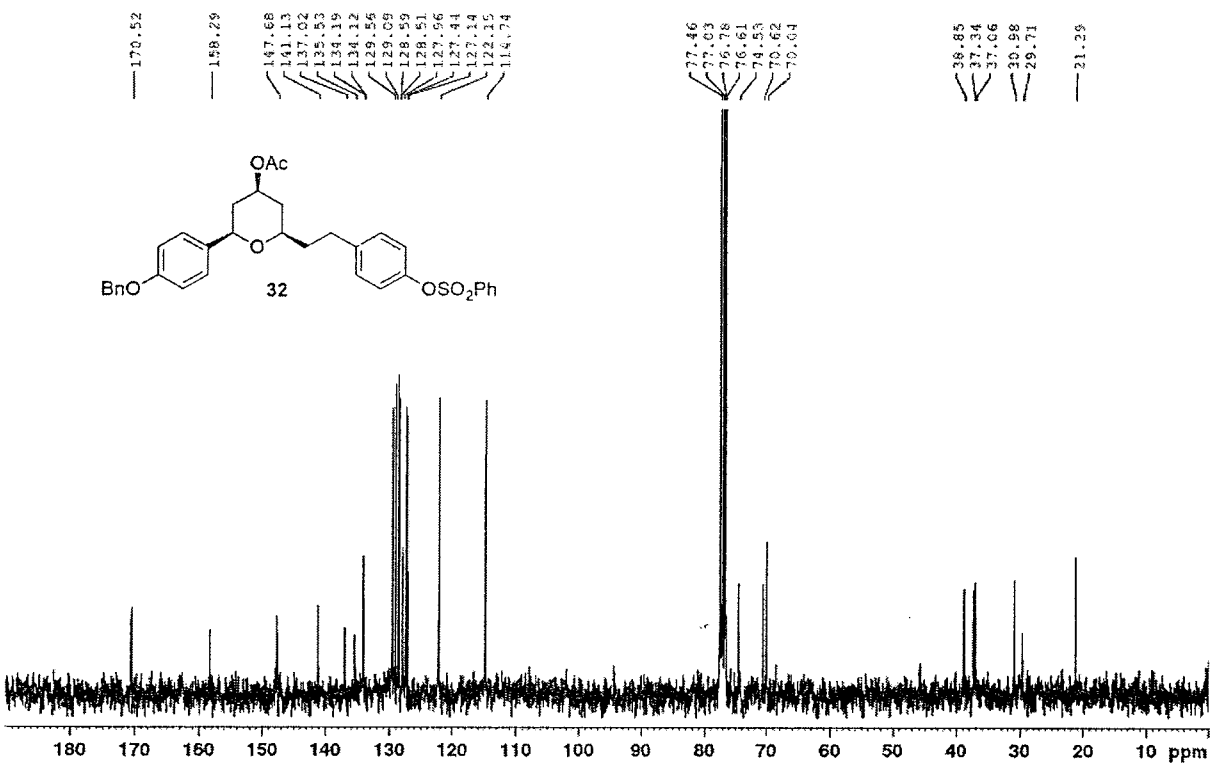
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **31ax**



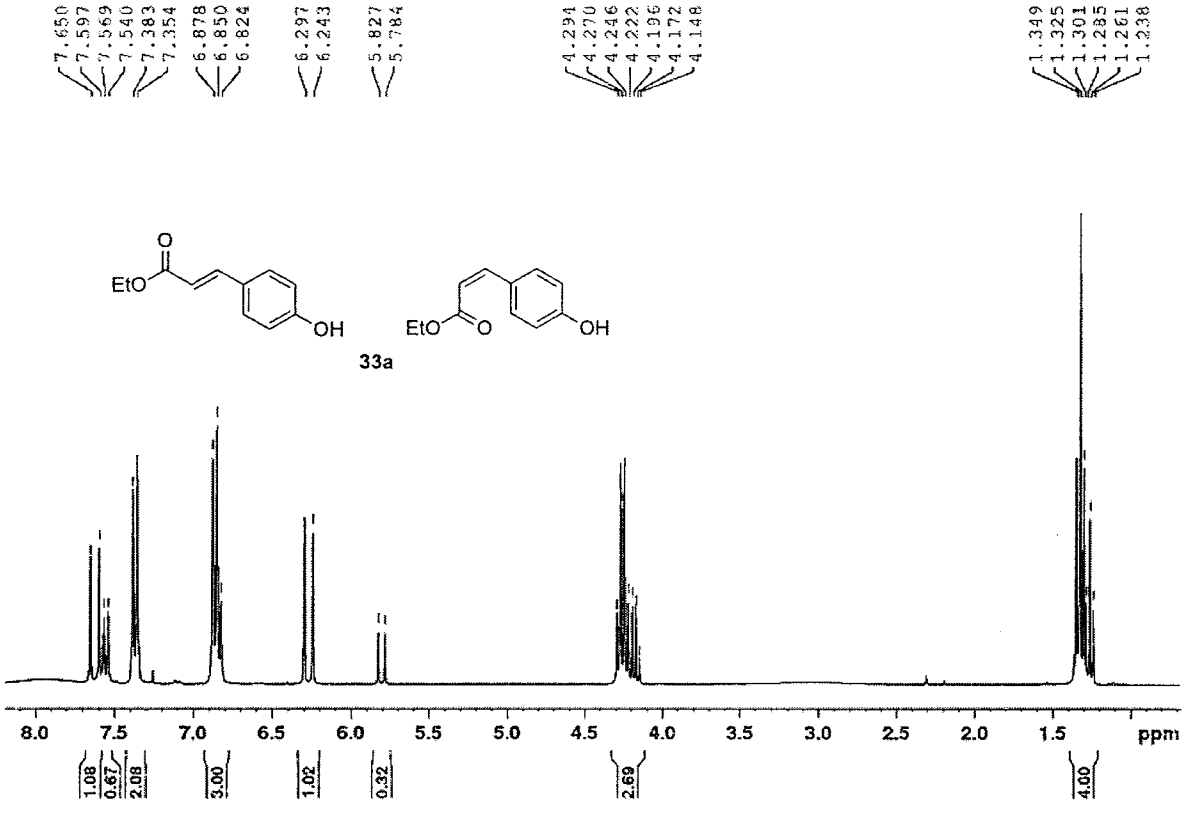
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **32**



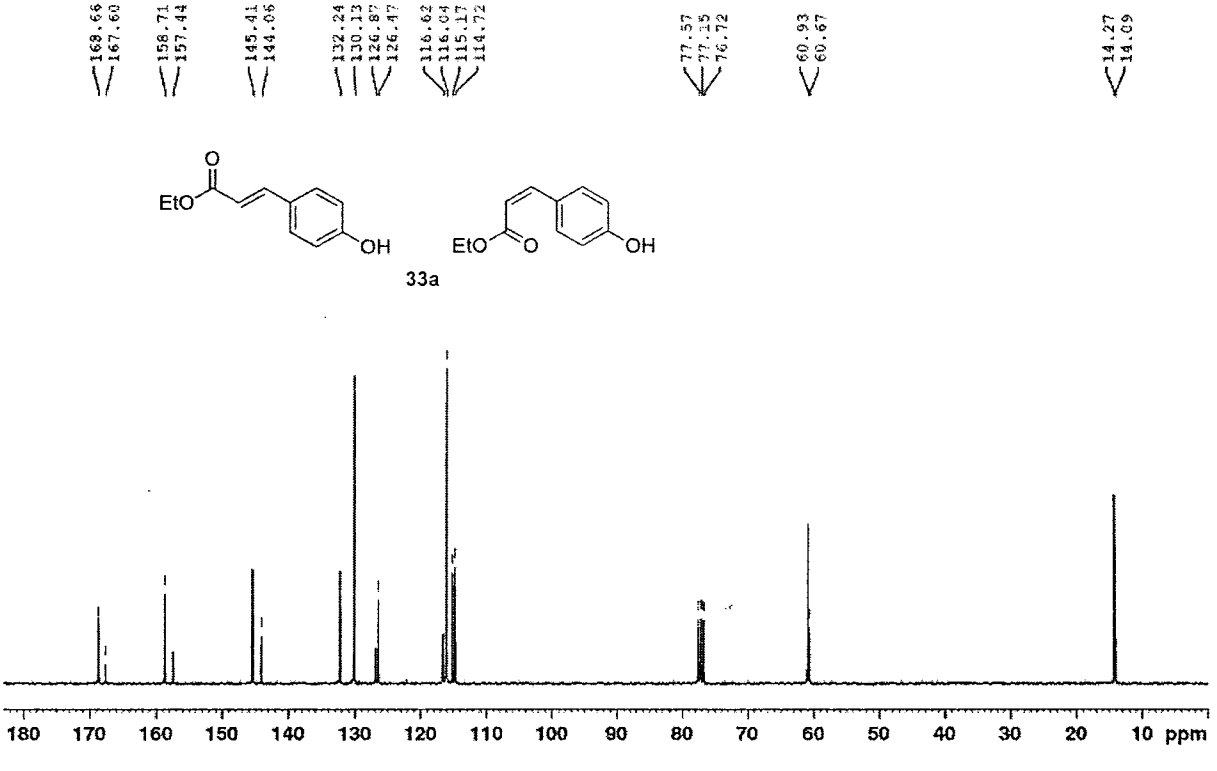
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **32**



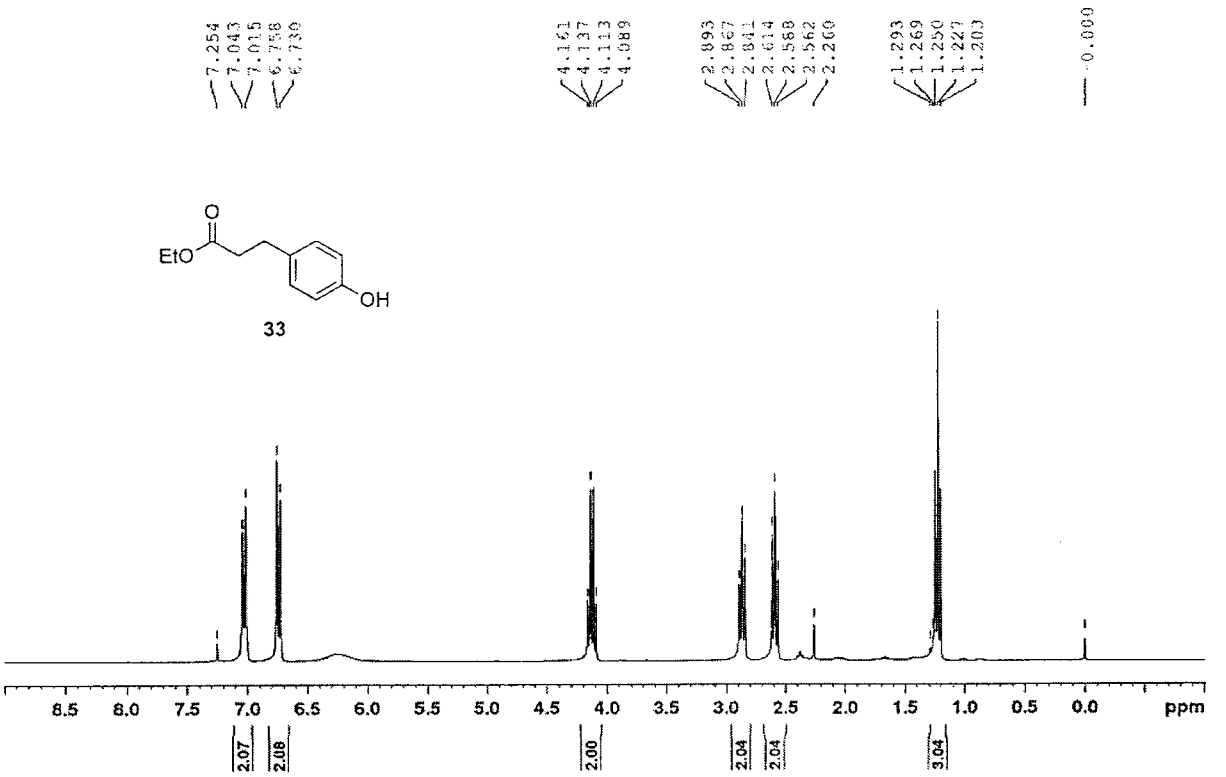
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ethyl 3-(4-hydroxyphenyl)acrylate (**33a**)



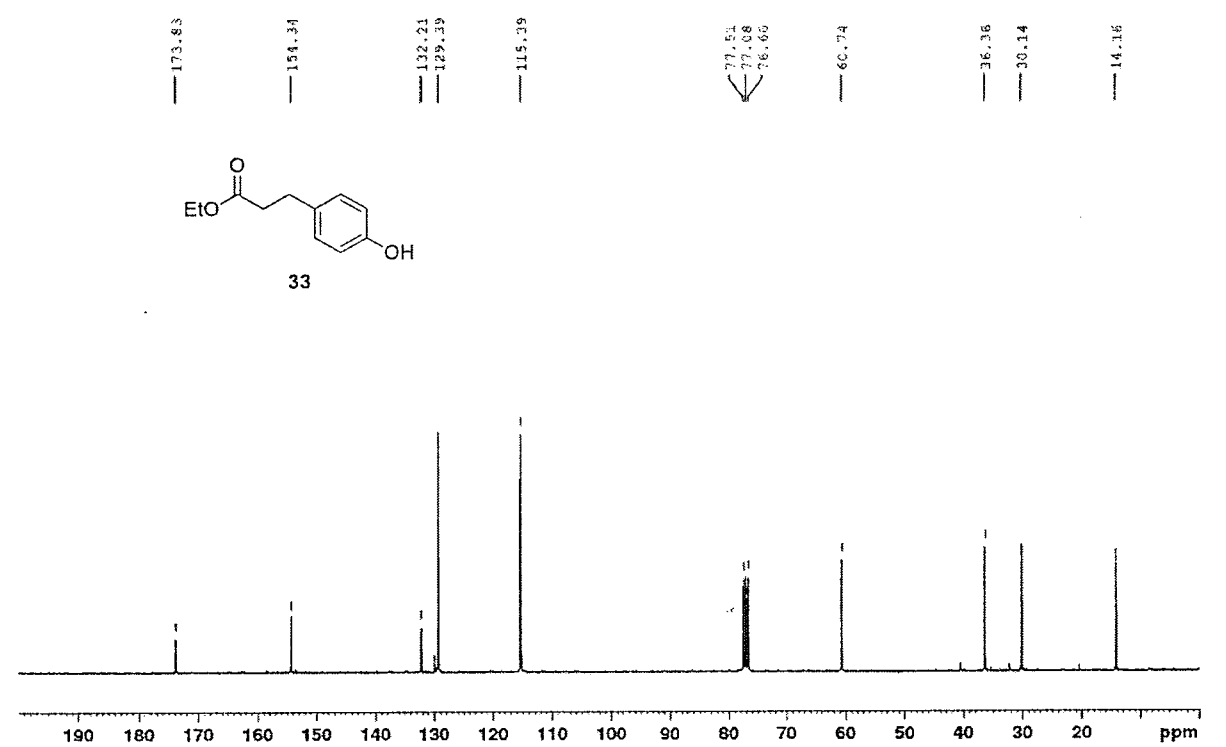
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ethyl 3-(4-hydroxyphenyl)acrylate (**33a**)



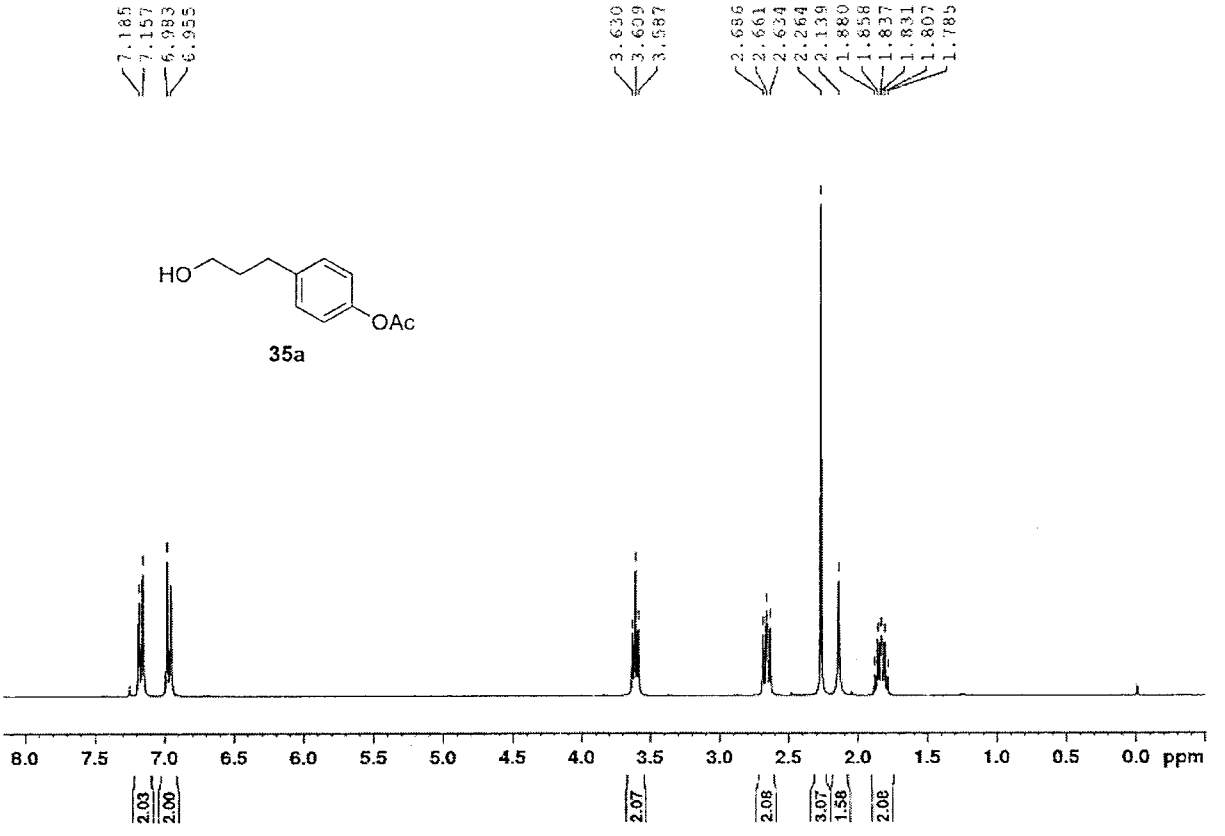
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of ethyl 3-(4-hydroxyphenyl)propanoate (**33**)



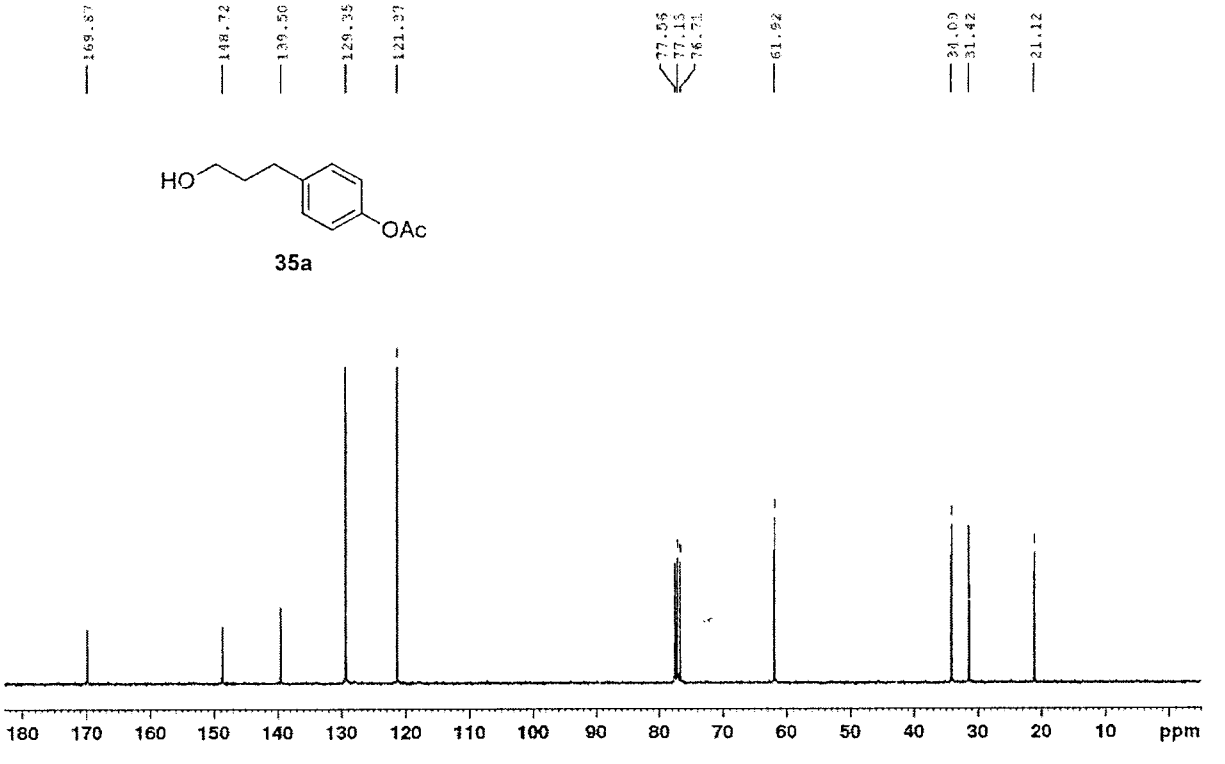
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of ethyl 3-(4-hydroxyphenyl)propanoate (**33**)



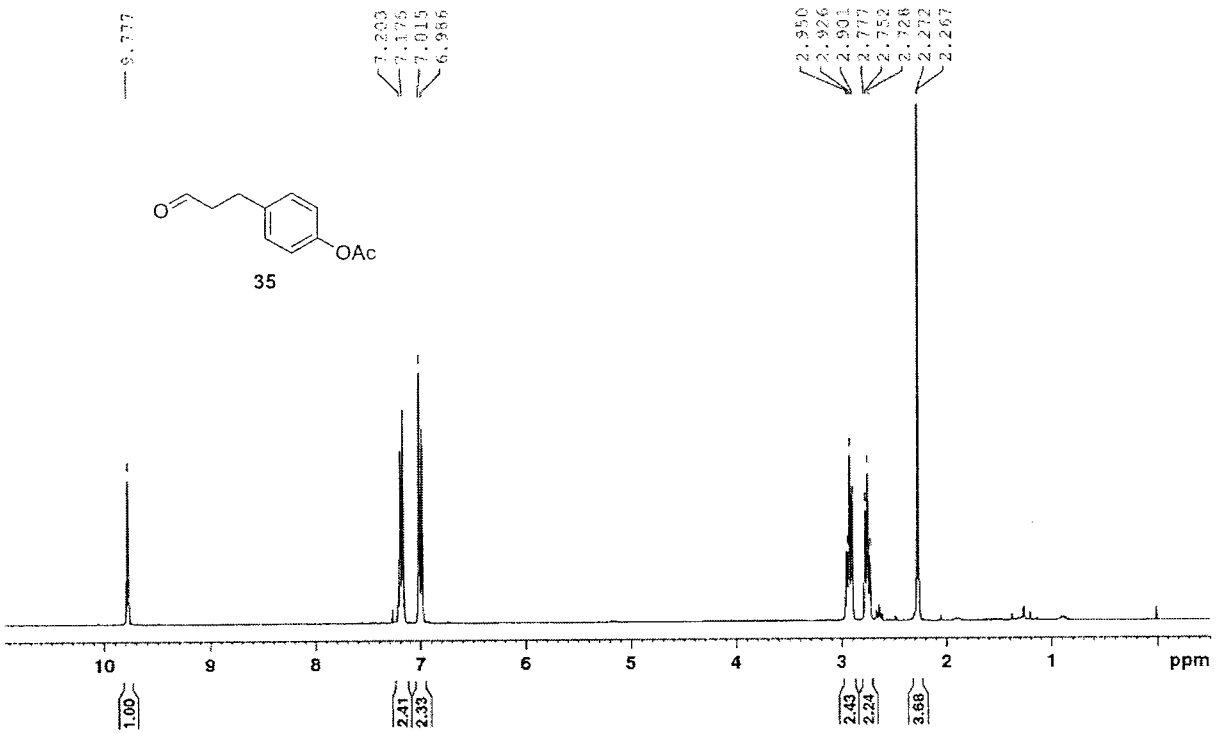
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of 4-(3-hydroxypropyl)phenyl acetate (**35a**)



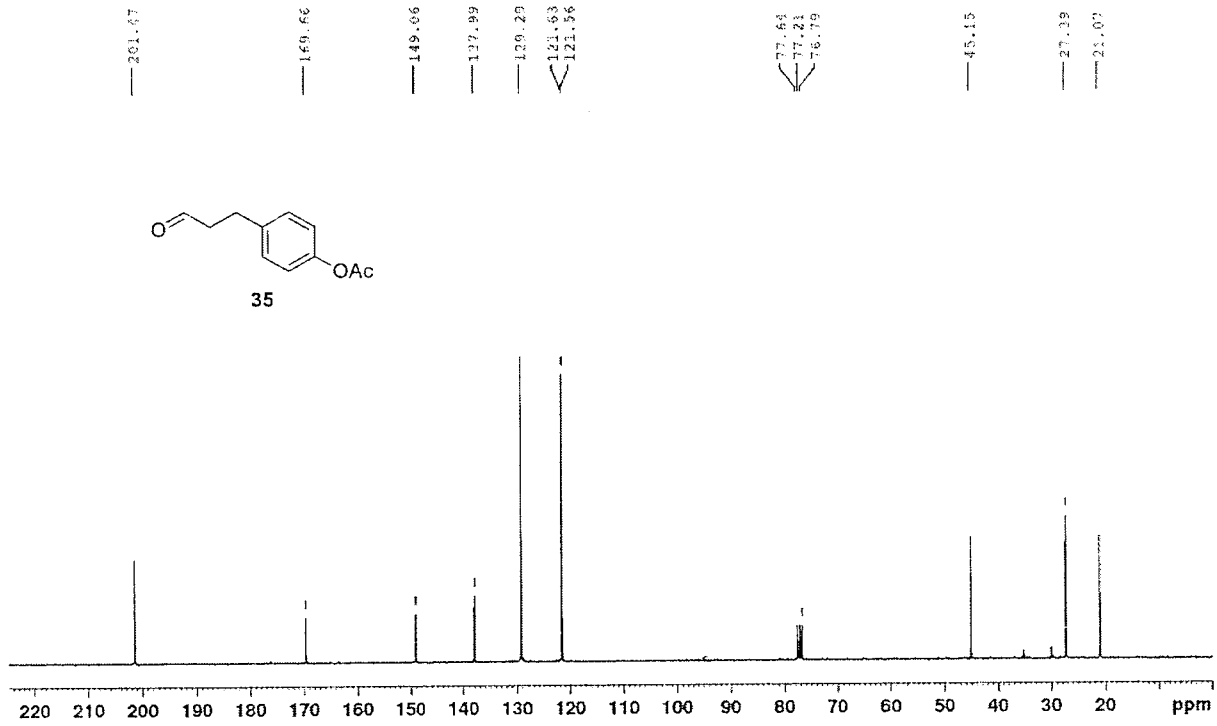
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of 4-(3-hydroxypropyl)phenyl acetate (**35a**)



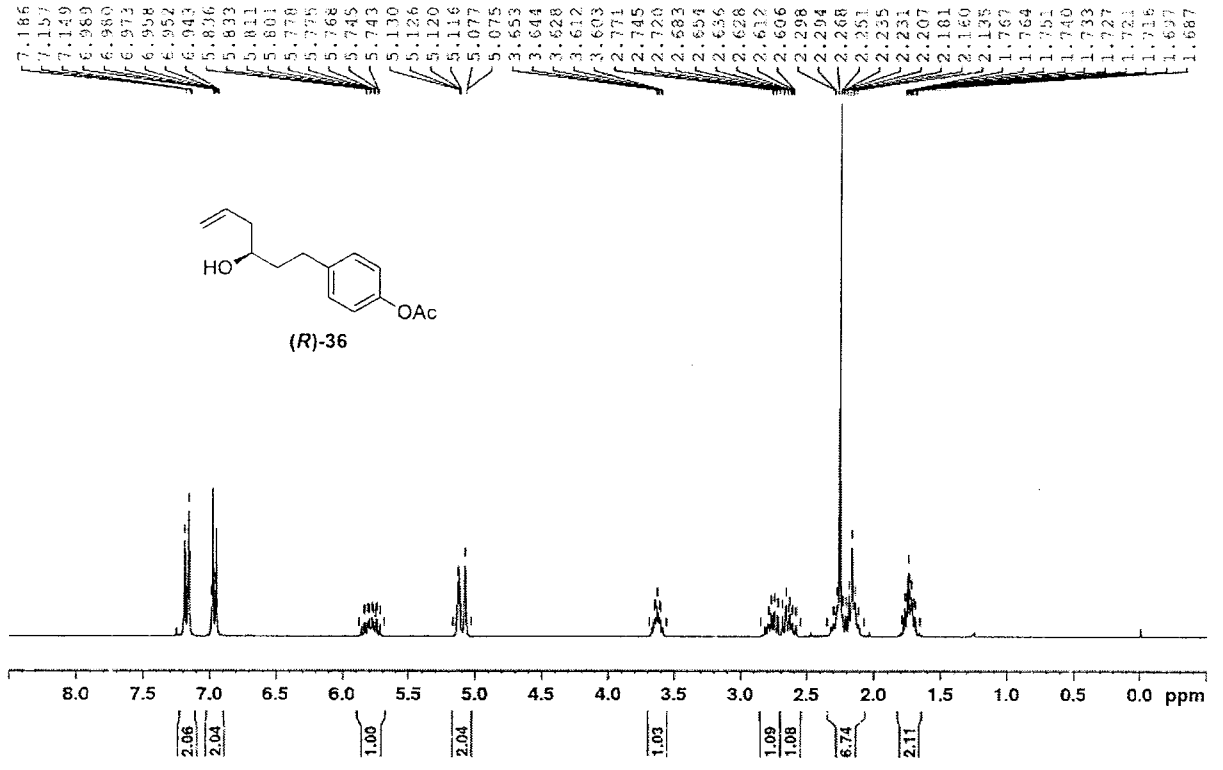
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of 4-(3-oxopropyl)phenyl acetate (**35**)



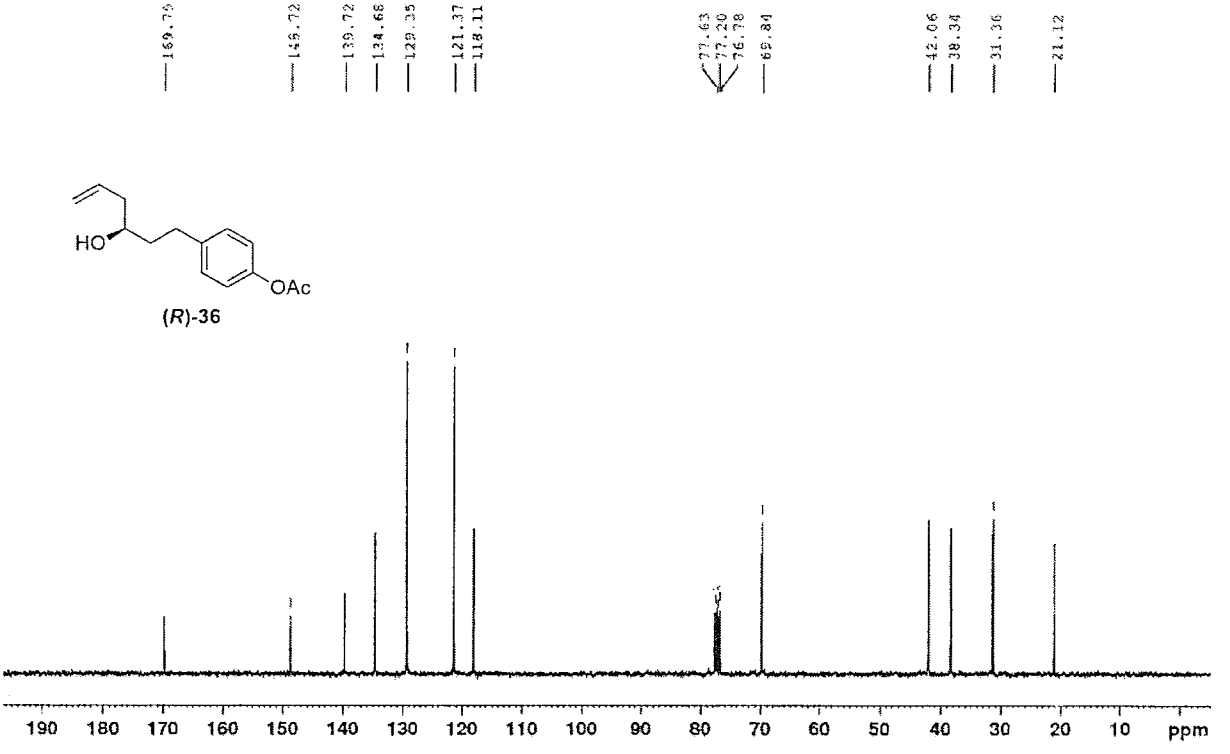
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of 4-(3-oxopropyl)phenyl acetate (**35**)



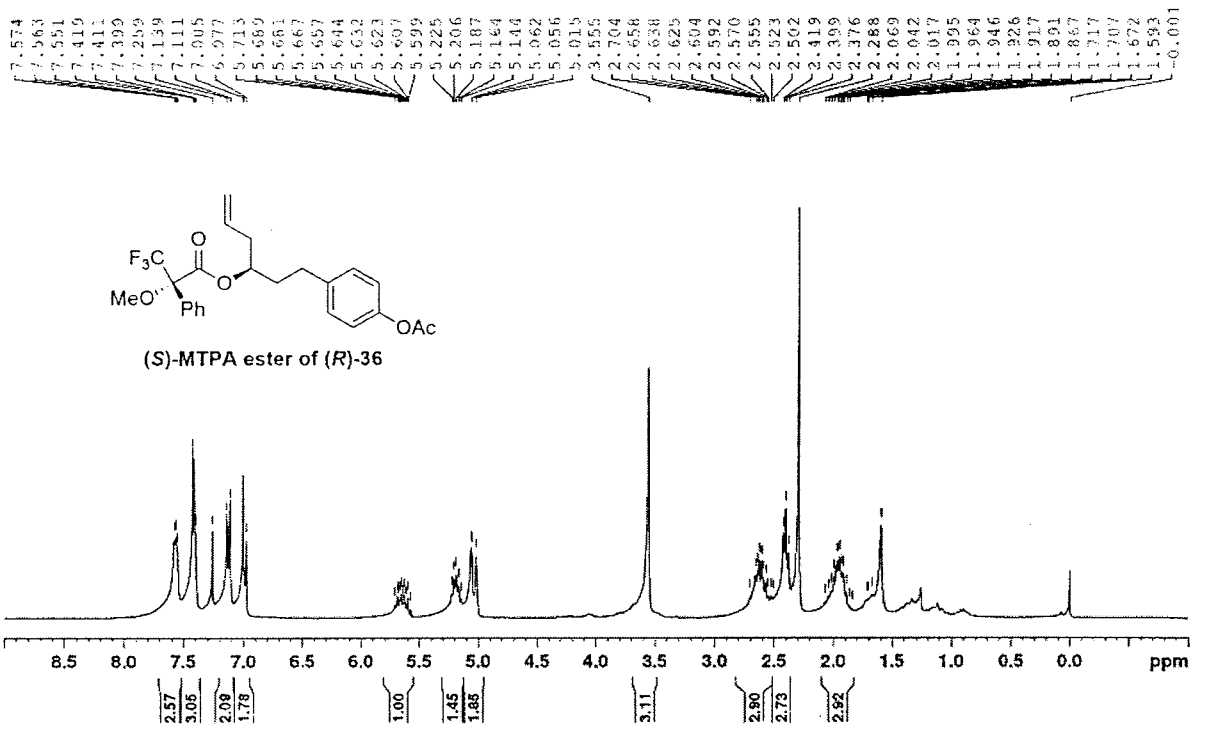
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*R*)-4-(3-hydroxyhex-5-enyl)phenyl acetate ((***R***)-**36**)



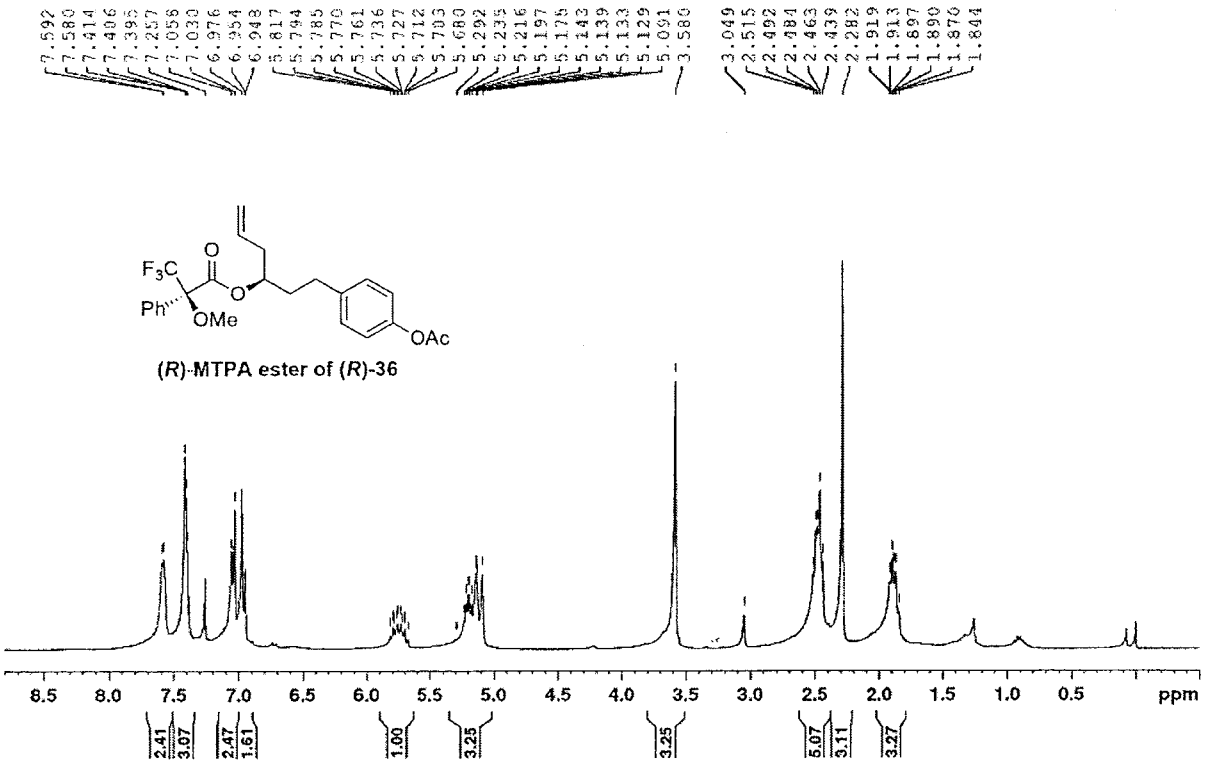
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of (*R*)-4-(3-hydroxyhex-5-enyl)phenyl acetate ((***R***)-**36**)



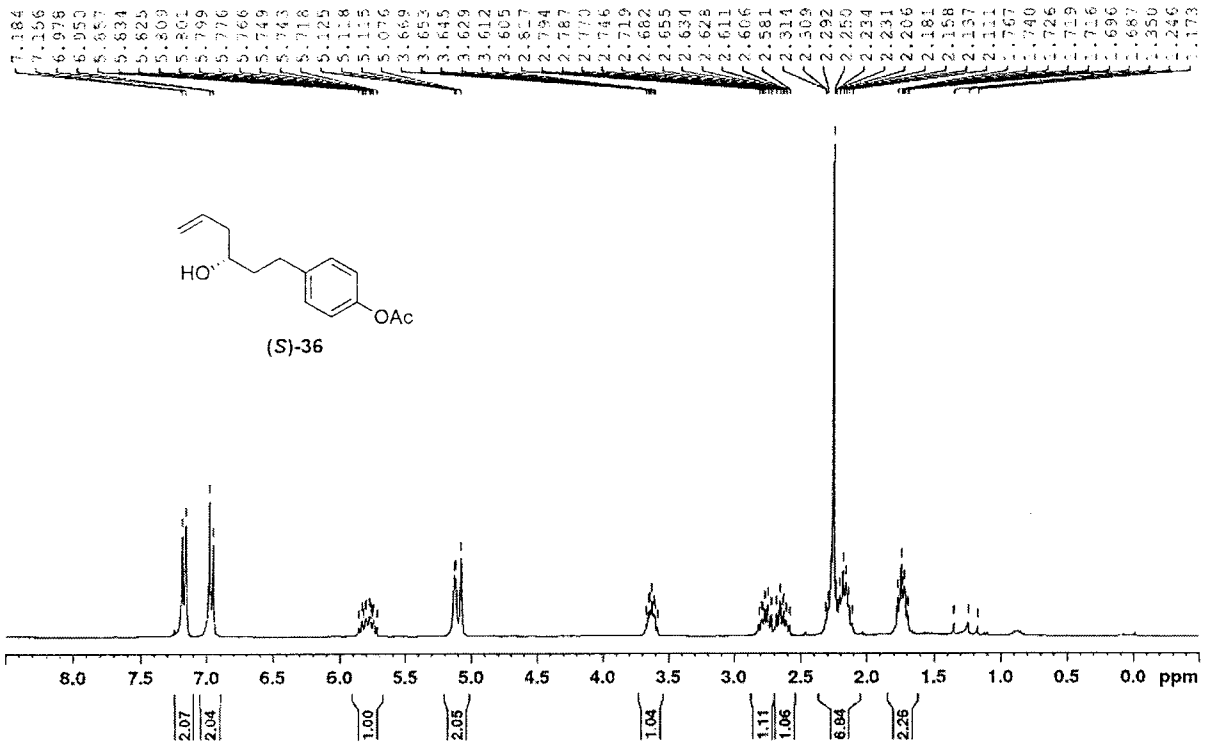
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*S*)-MTPA ester of **(*R*)-36**



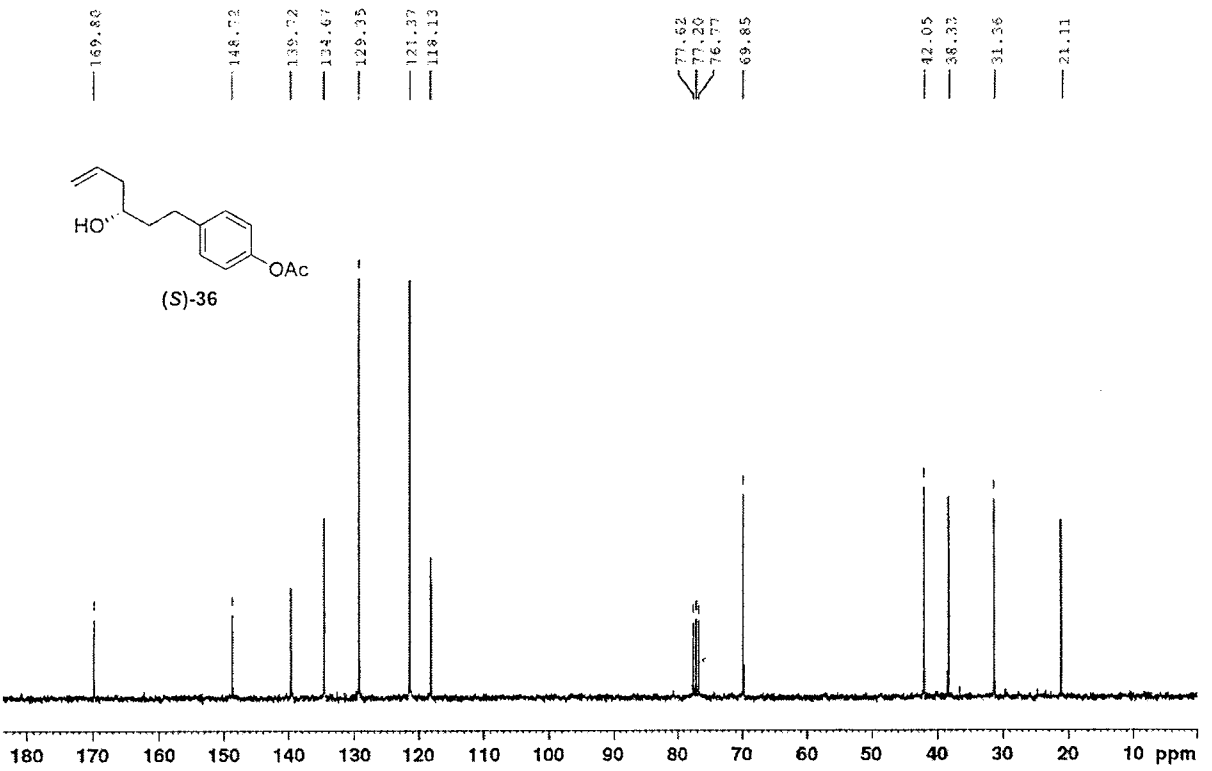
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*R*)-MTPA ester of **(*R*)-36**



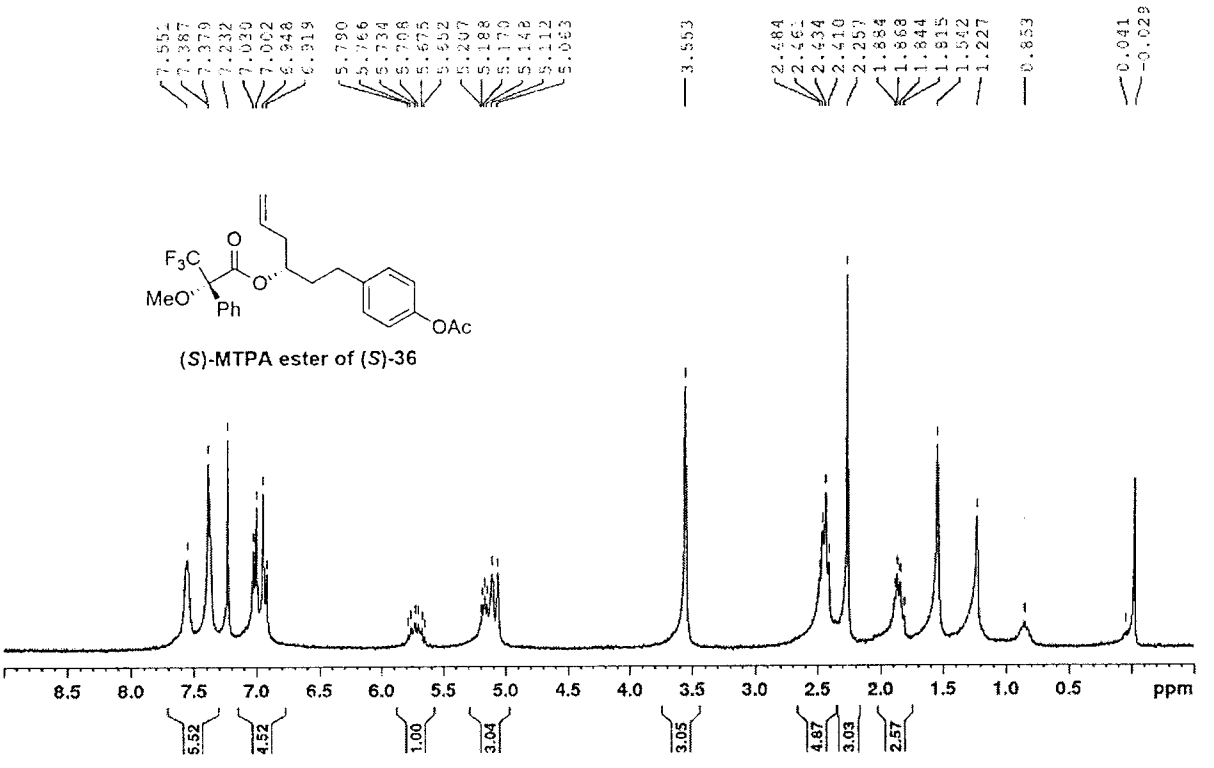
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*S*)-4-(3-hydroxyhex-5-enyl)phenyl acetate ((***S*****)-36**)



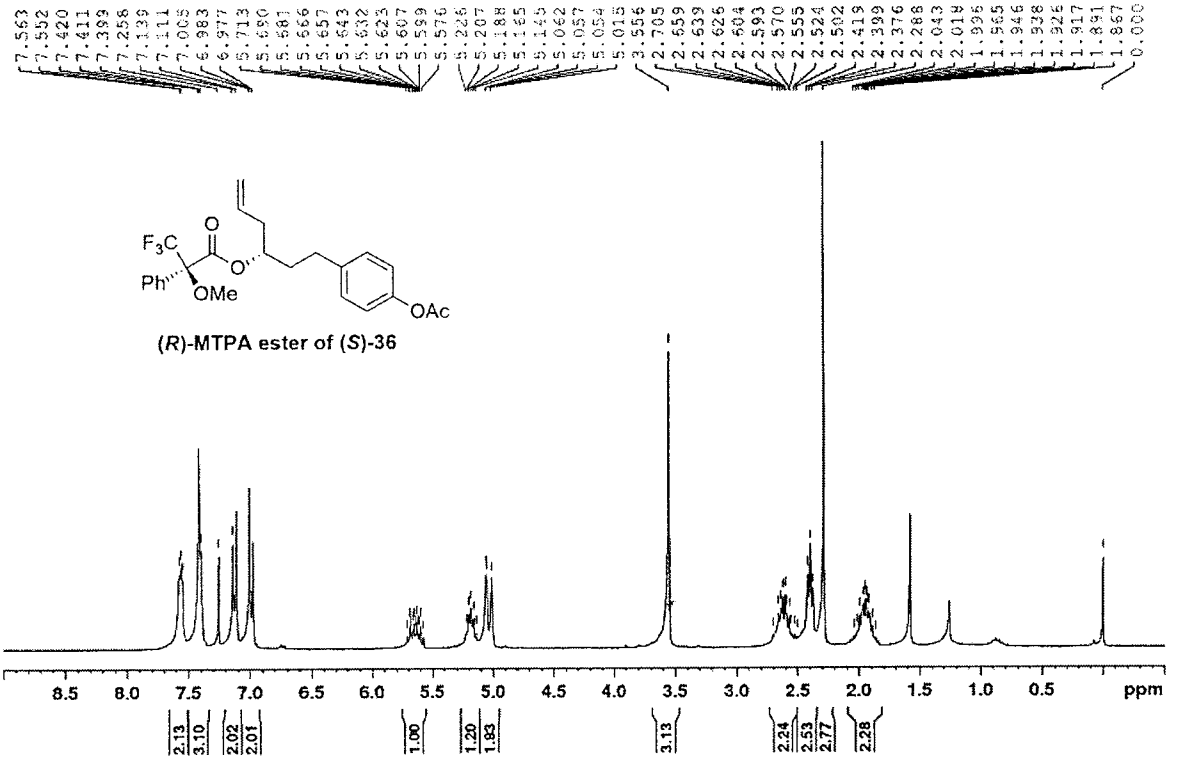
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of (*S*)-4-(3-hydroxyhex-5-enyl)phenyl acetate ((***S*****)-36**)



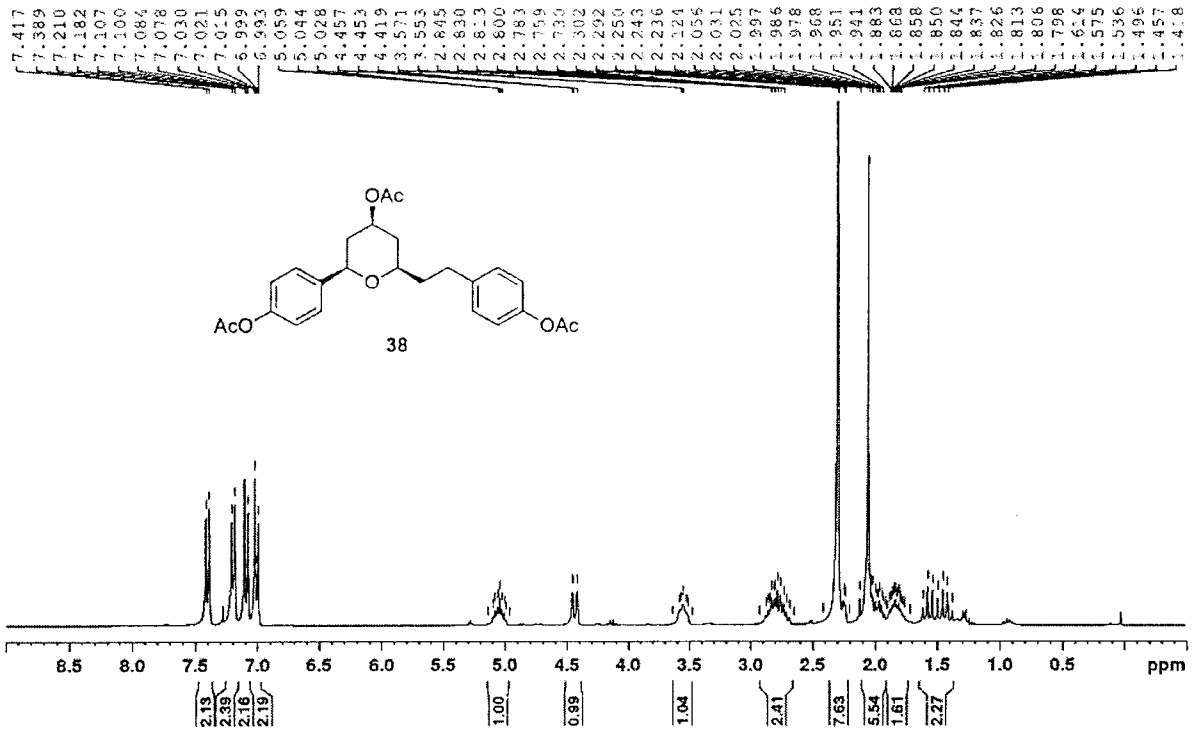
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*S*)-MTPA ester of **(*S*)-36**



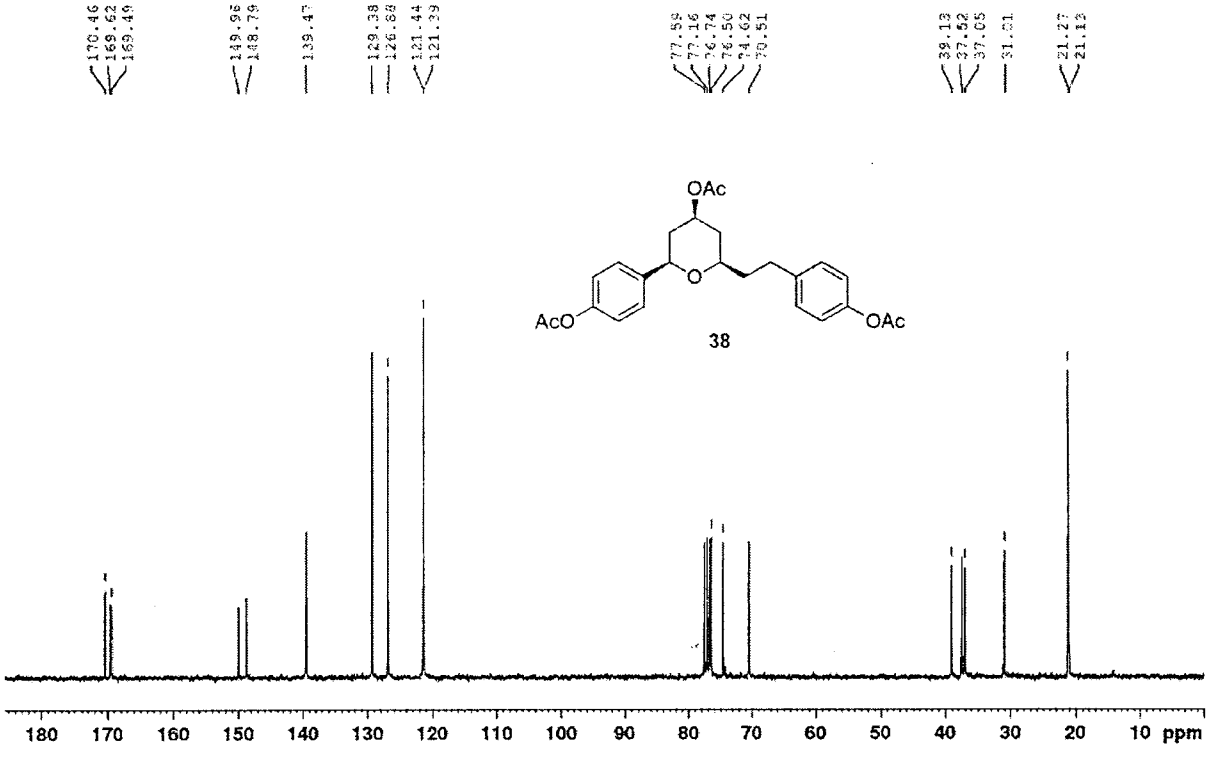
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of (*R*)-MTPA ester of **(*S*)-36**



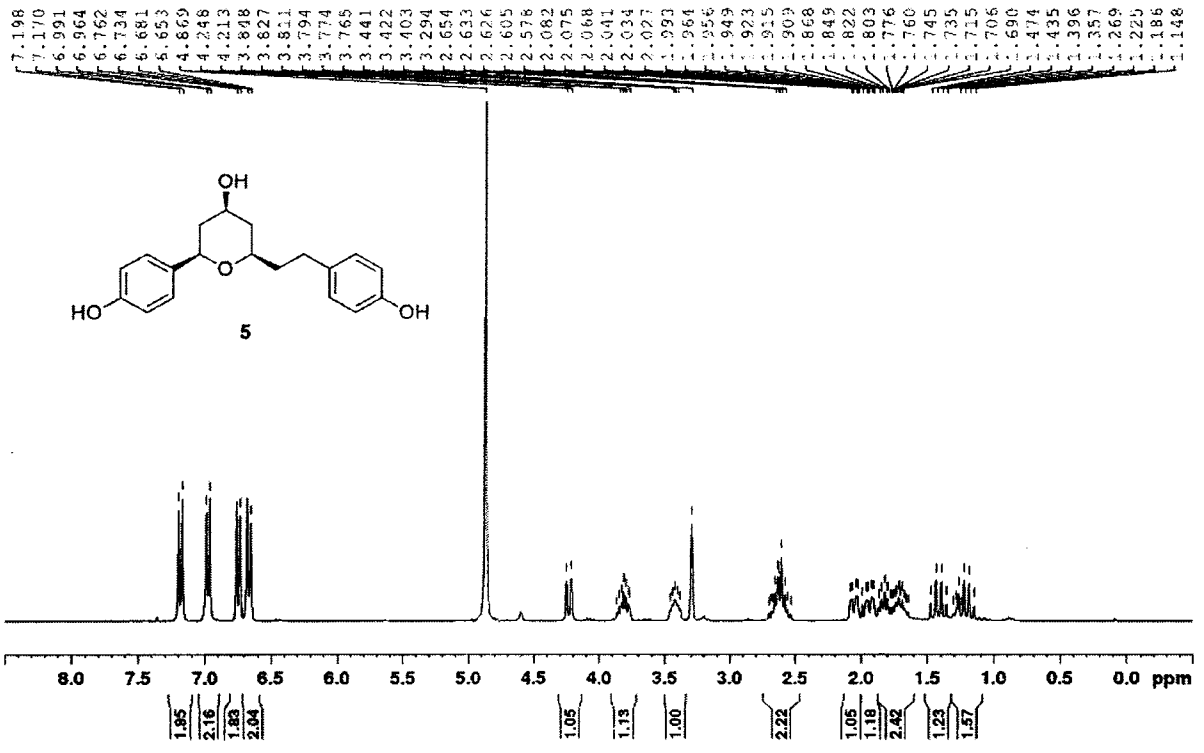
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **38**



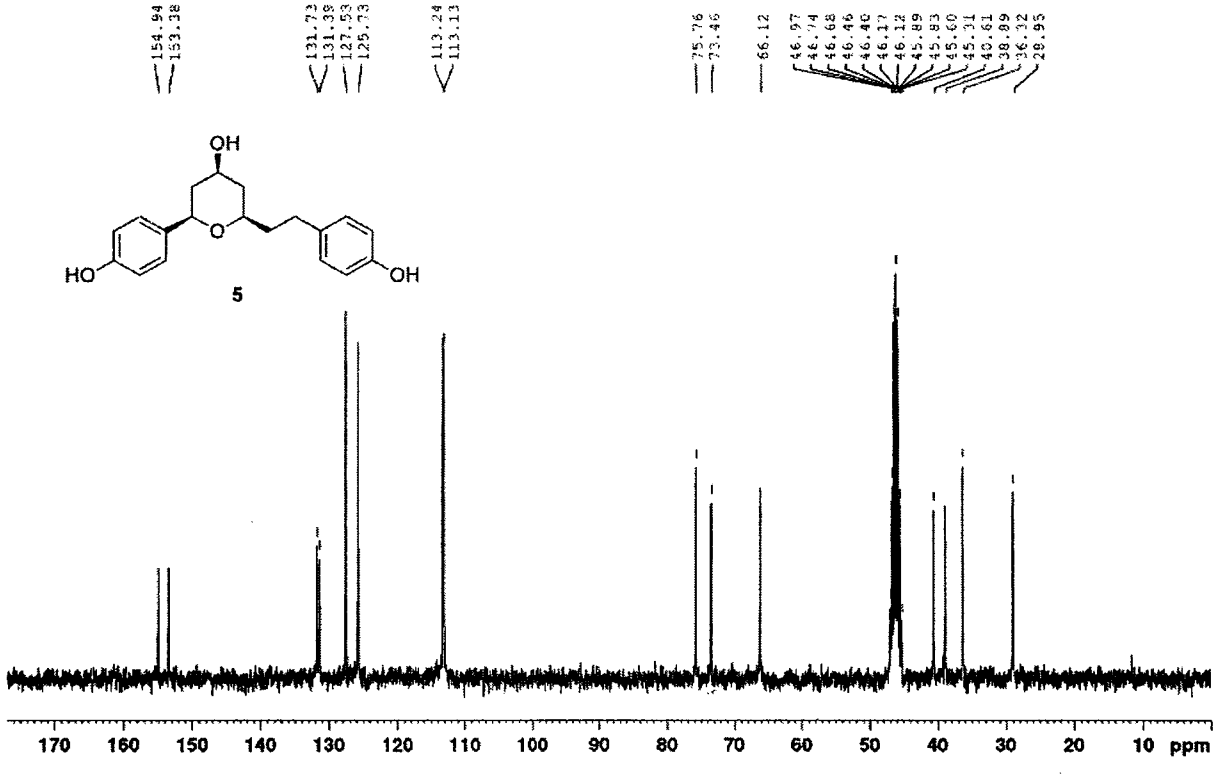
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **38**



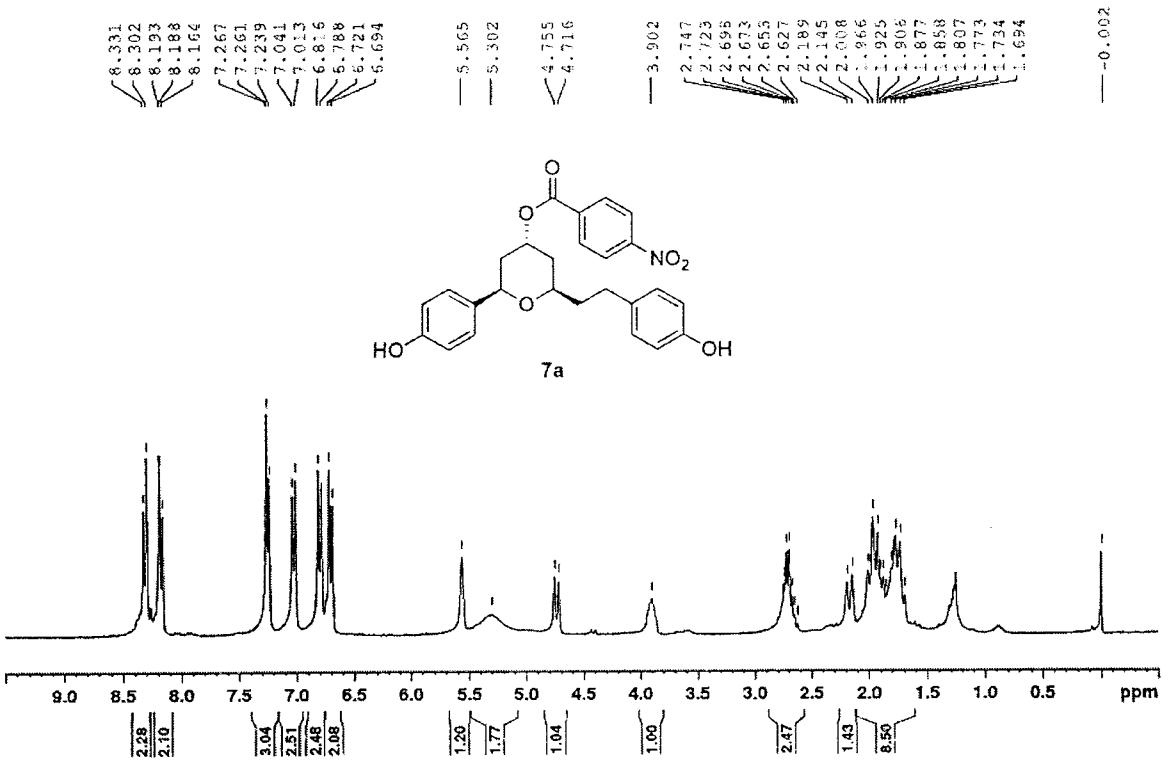
^{1}H NMR (300 MHz, CD_3OD) spectrum of diarylheptanoid **5**



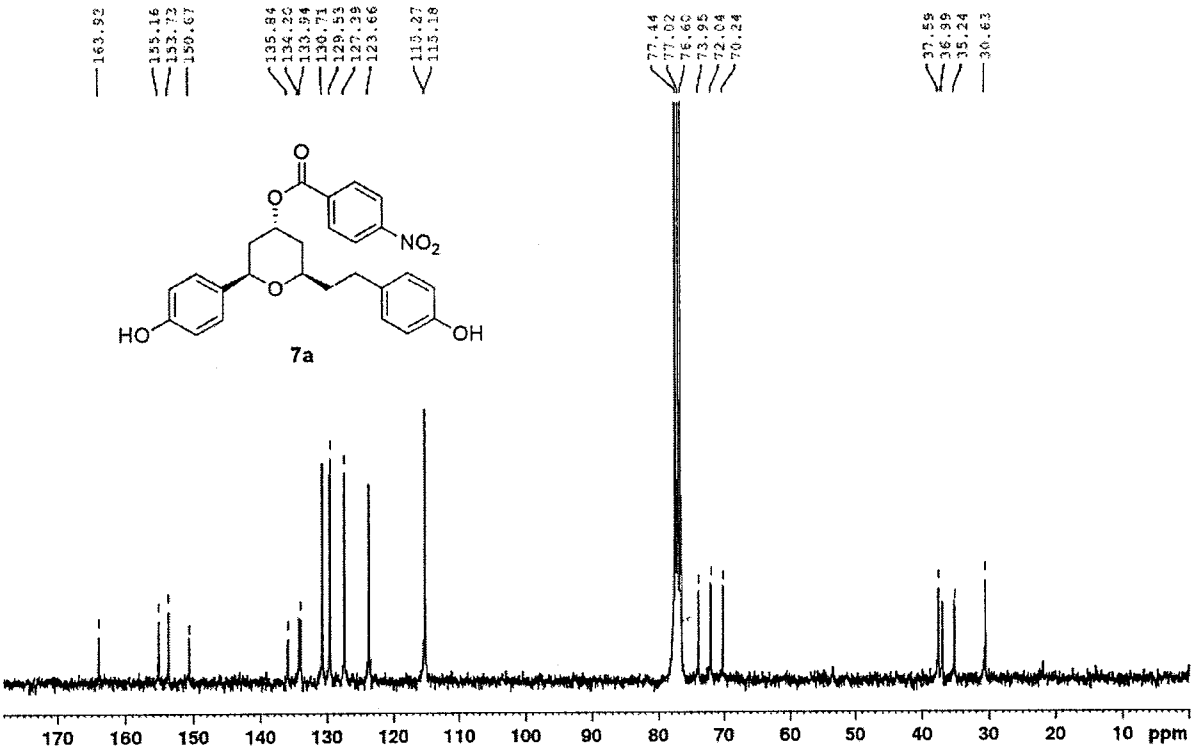
^{13}C NMR (75 MHz, CD_3OD) spectrum of diarylheptanoid **5**



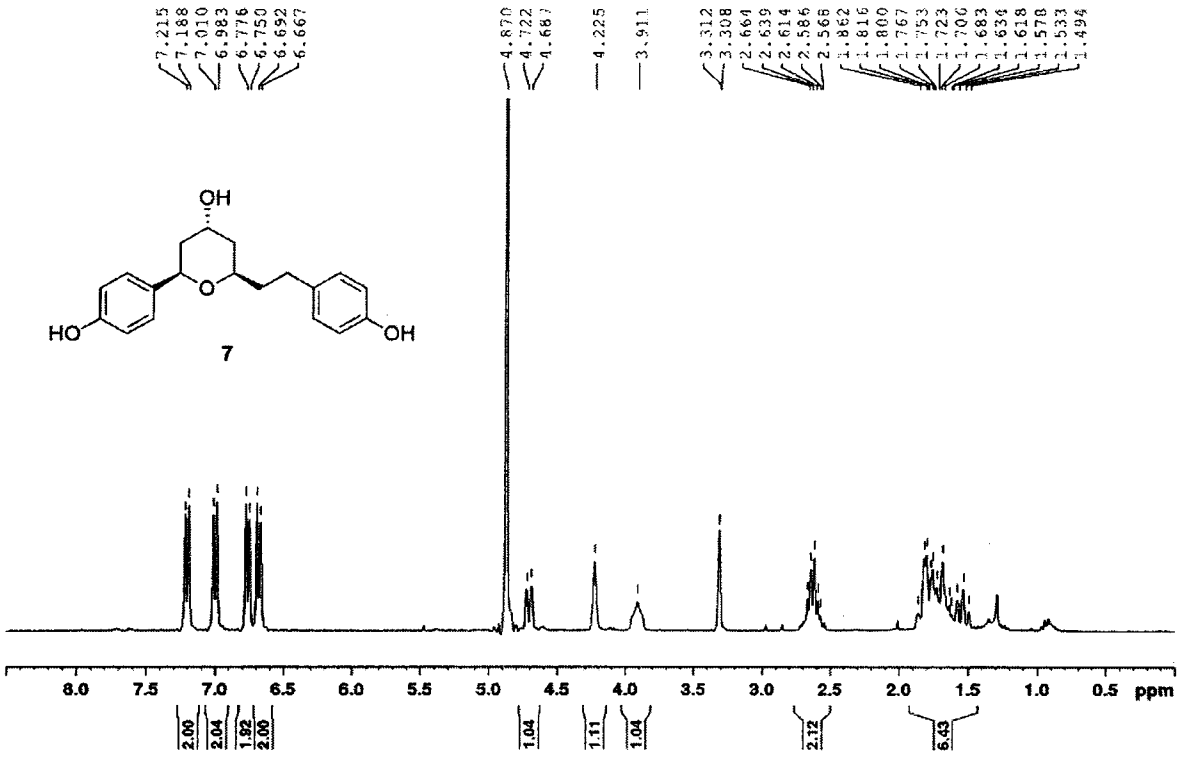
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7a**



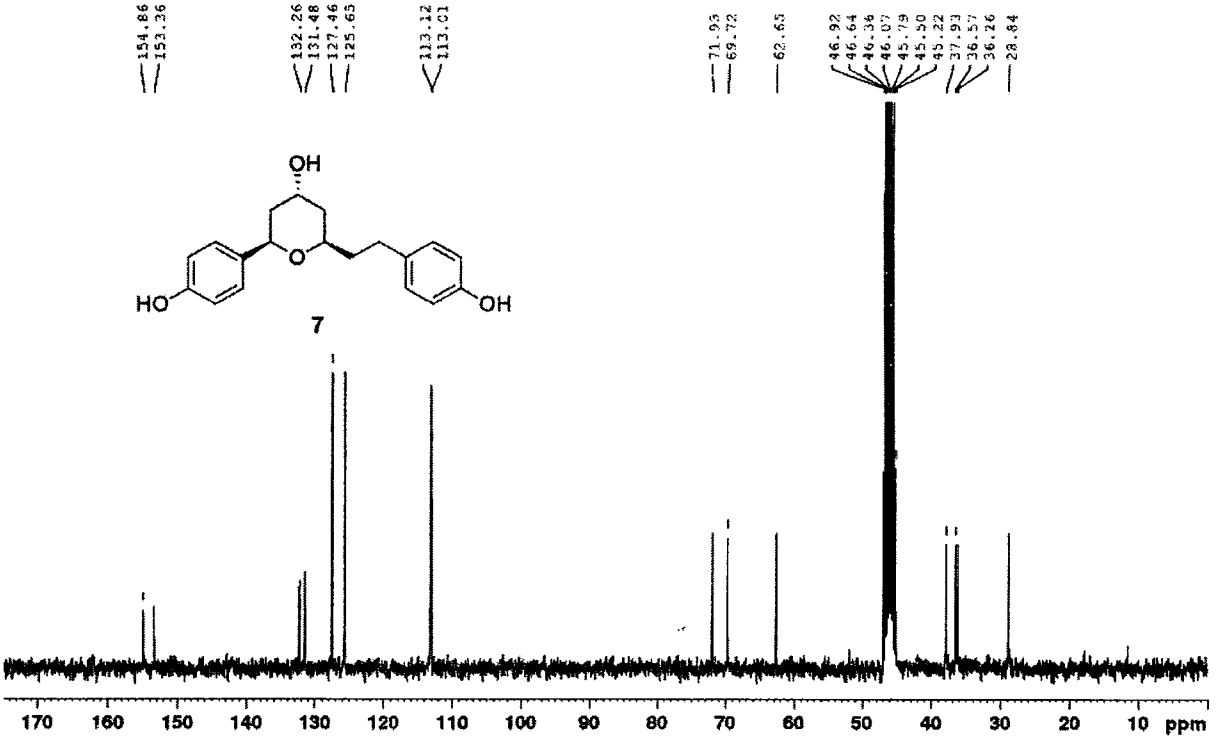
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **7a**



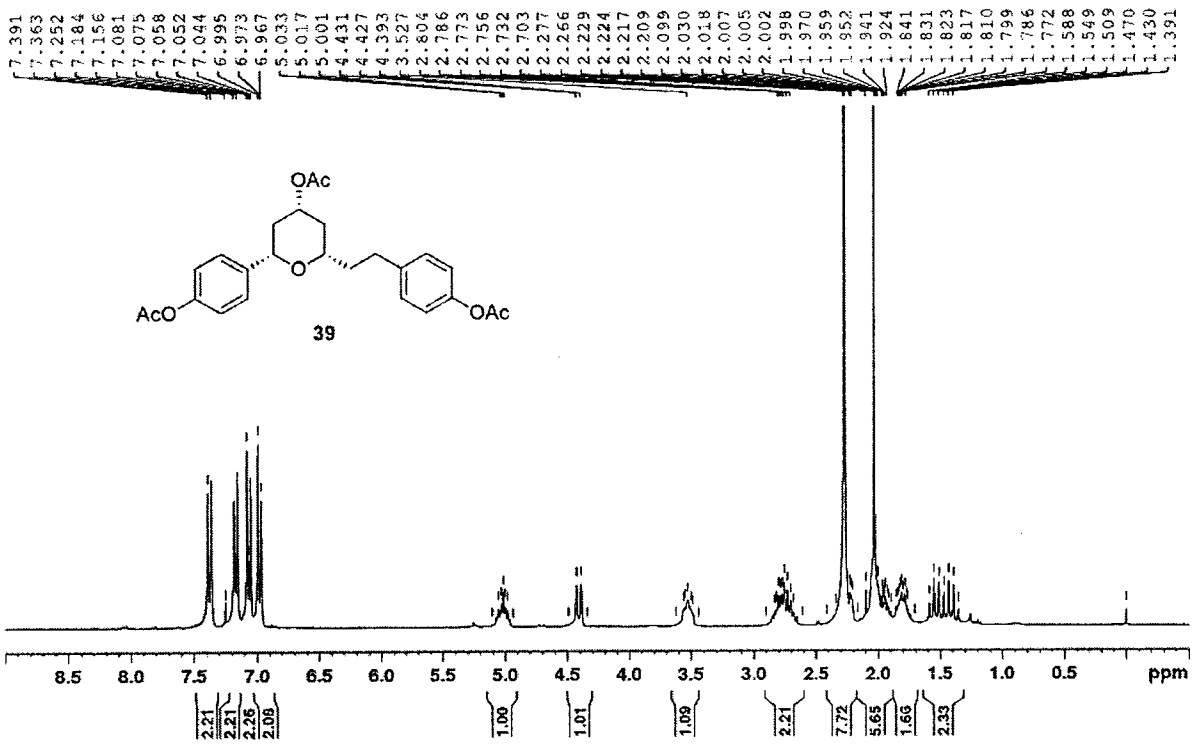
^{1}H NMR (300 MHz, CD_3OD) spectrum of diarylheptanoid 7



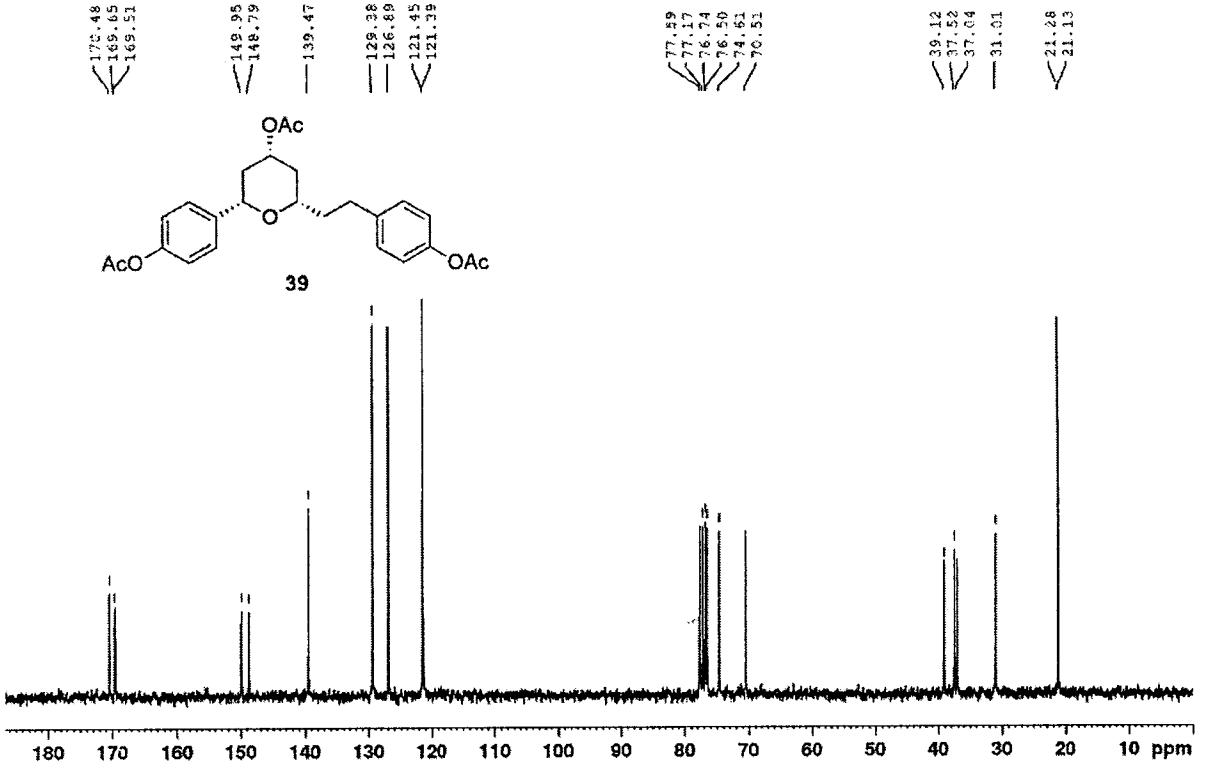
^{13}C NMR (75 MHz, CD_3OD) spectrum of diarylheptanoid 7



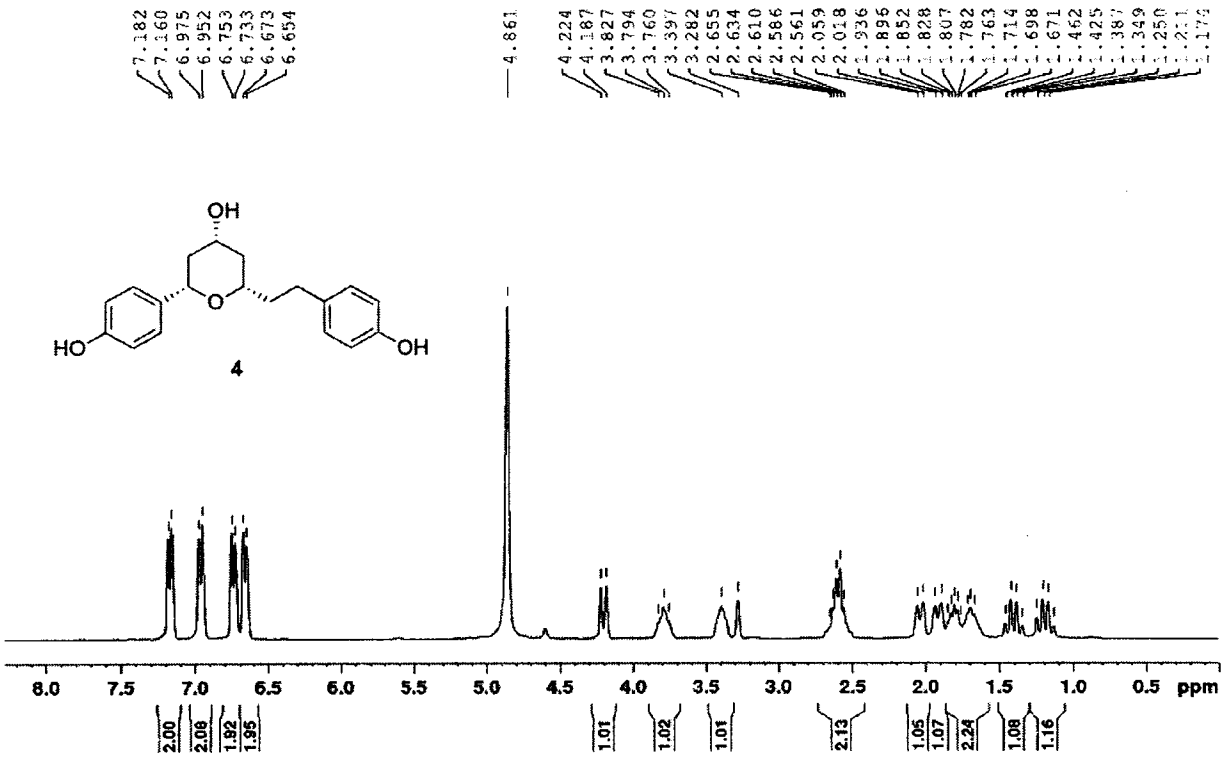
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **39**



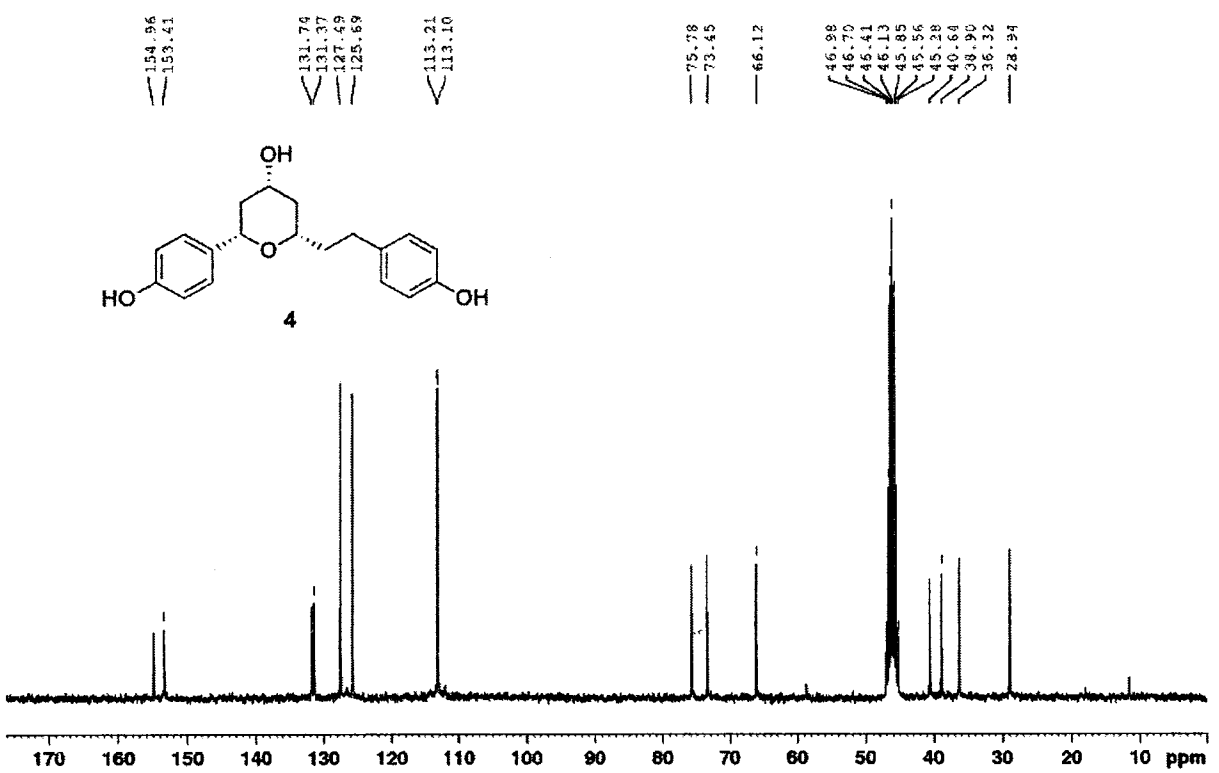
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **39**



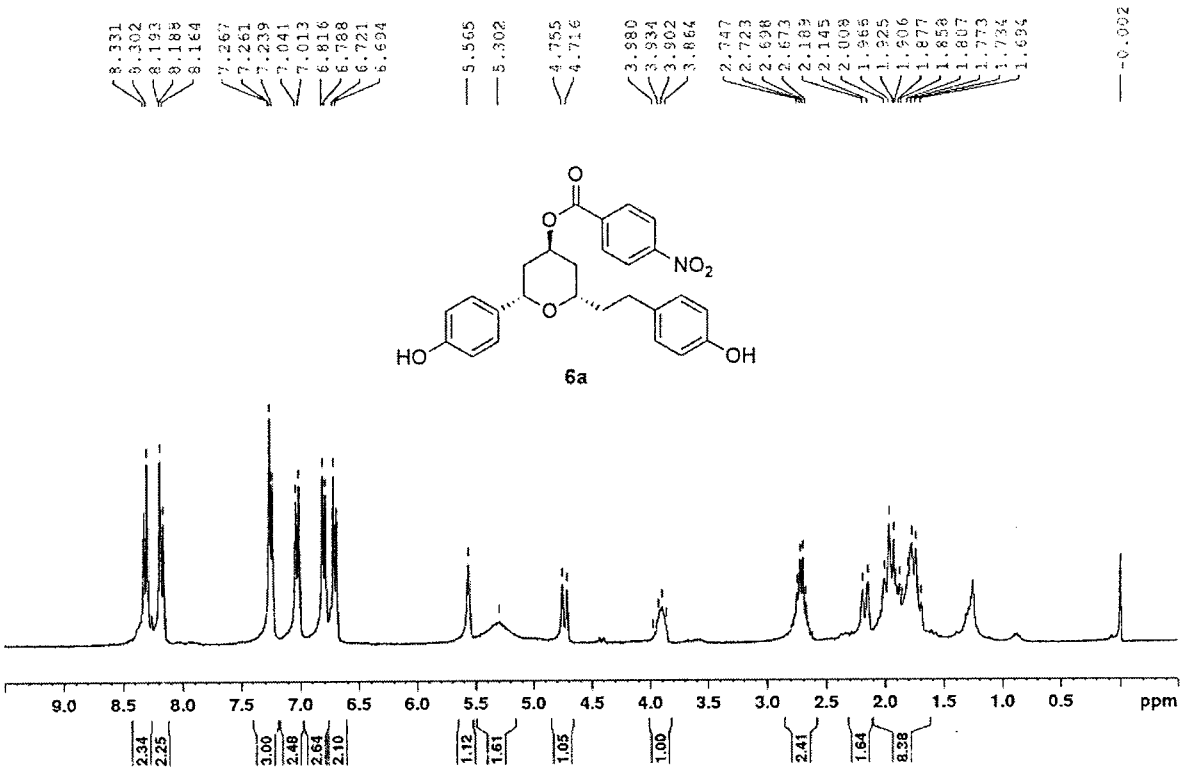
^{1}H NMR (300 MHz, CD_3OD) spectrum of diarylheptanoid **4**



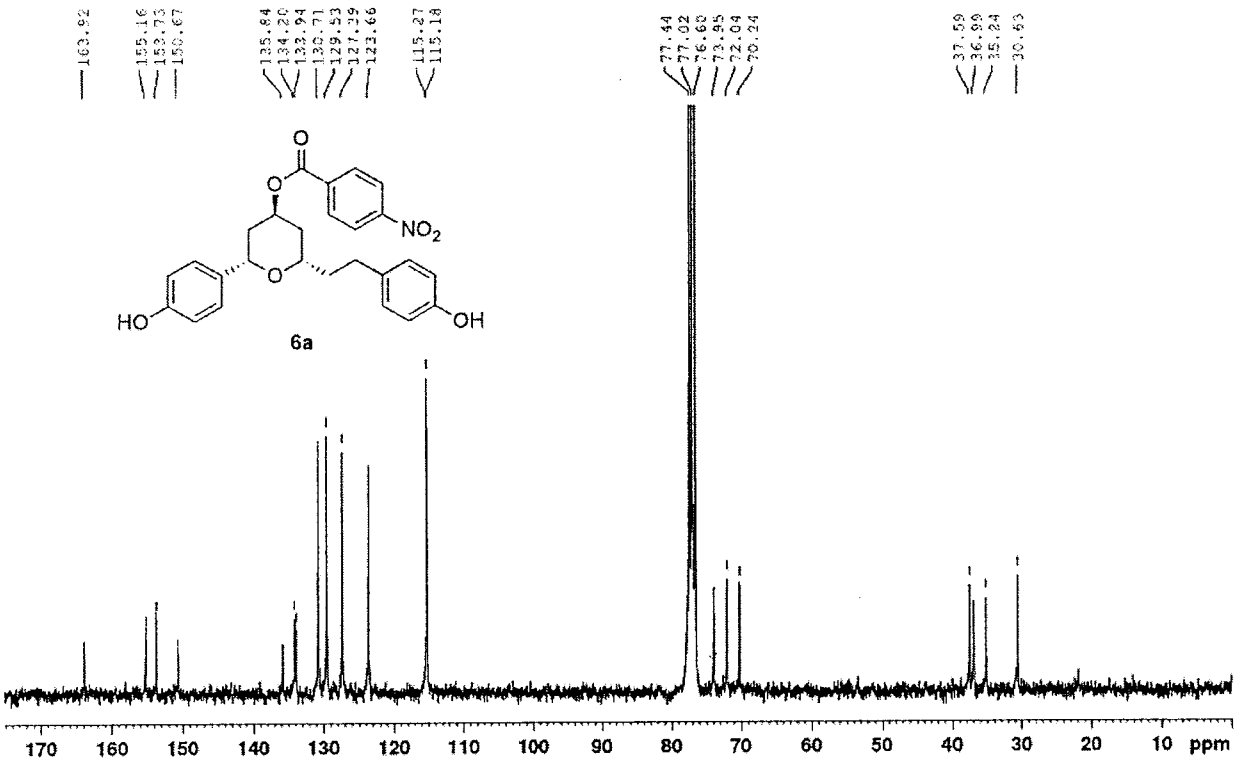
^{13}C NMR (75 MHz, CD_3OD) spectrum of diarylheptanoid **4**



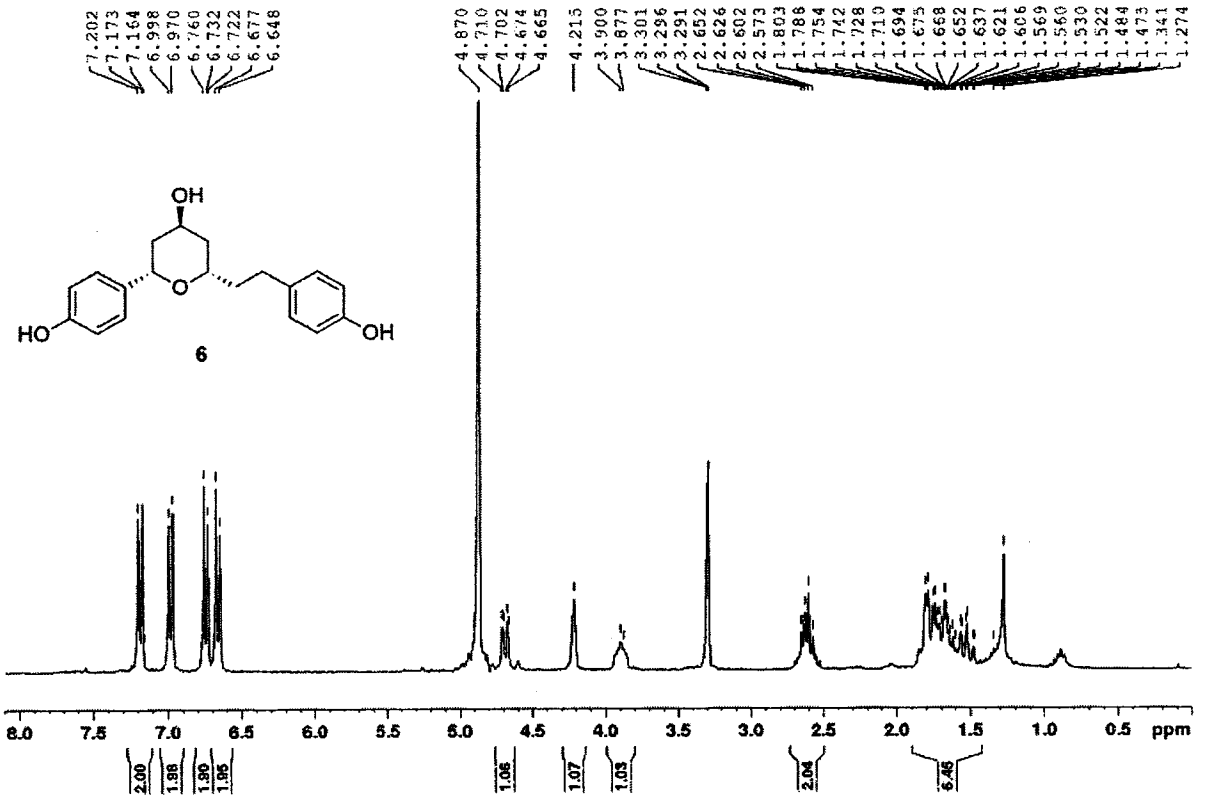
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **6a**



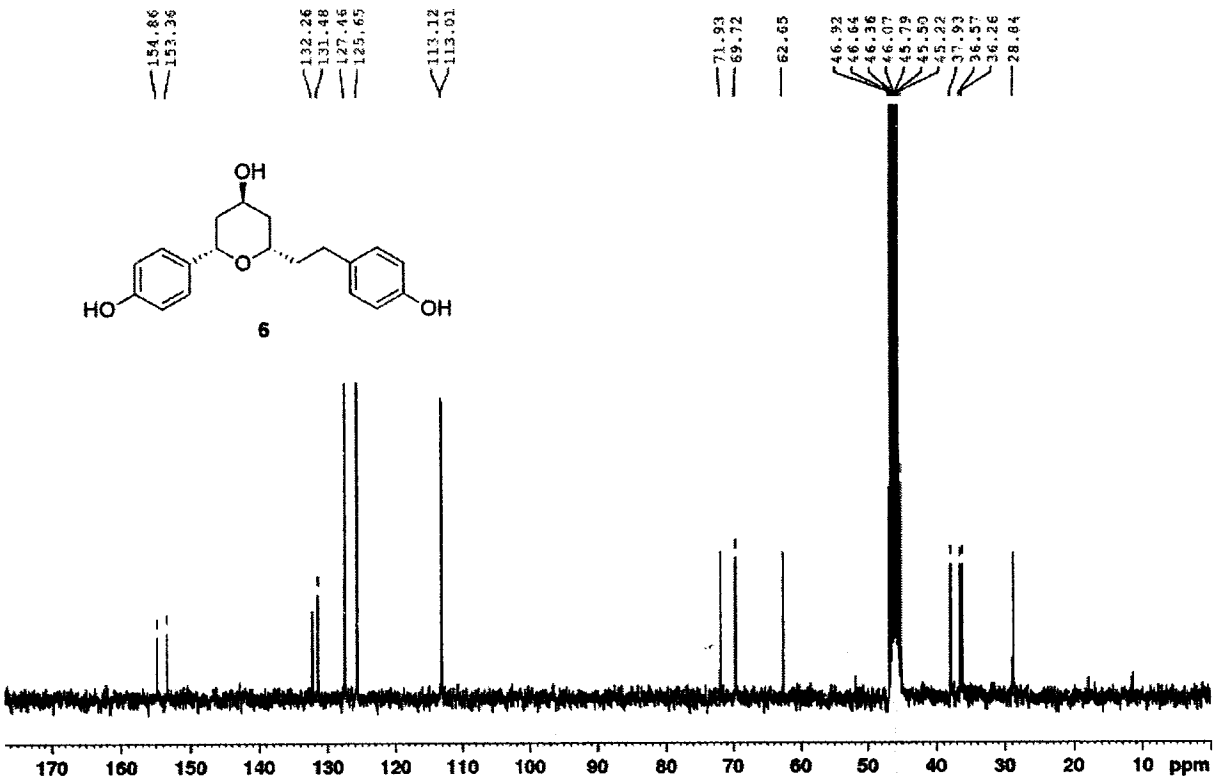
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **6a**



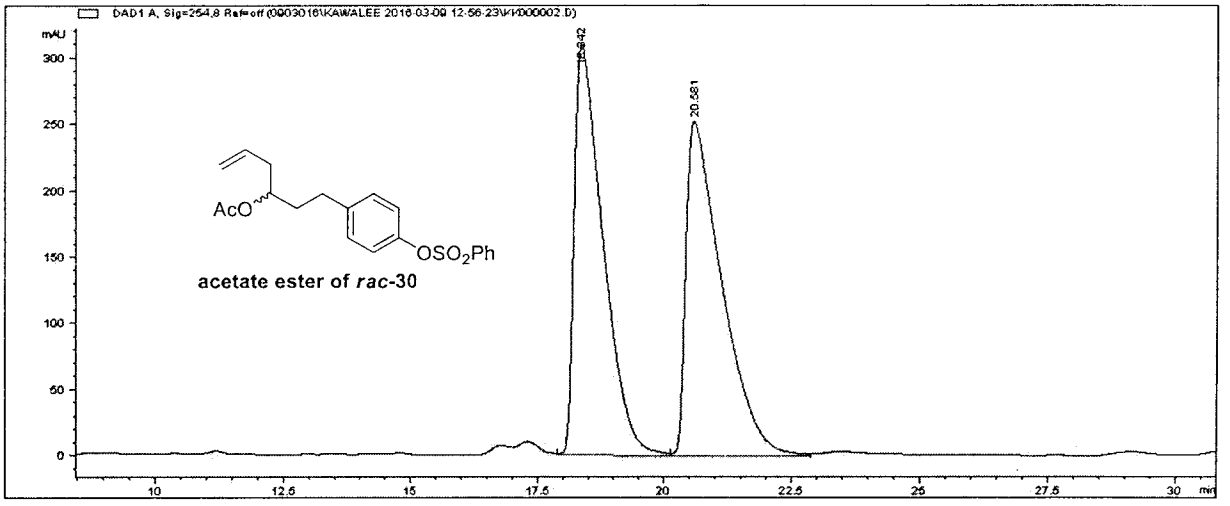
^{1}H NMR (300 MHz, CD_3OD) spectrum of diarylheptanoid **6**



^{13}C NMR (75 MHz, CD_3OD) spectrum of diarylheptanoid **6**

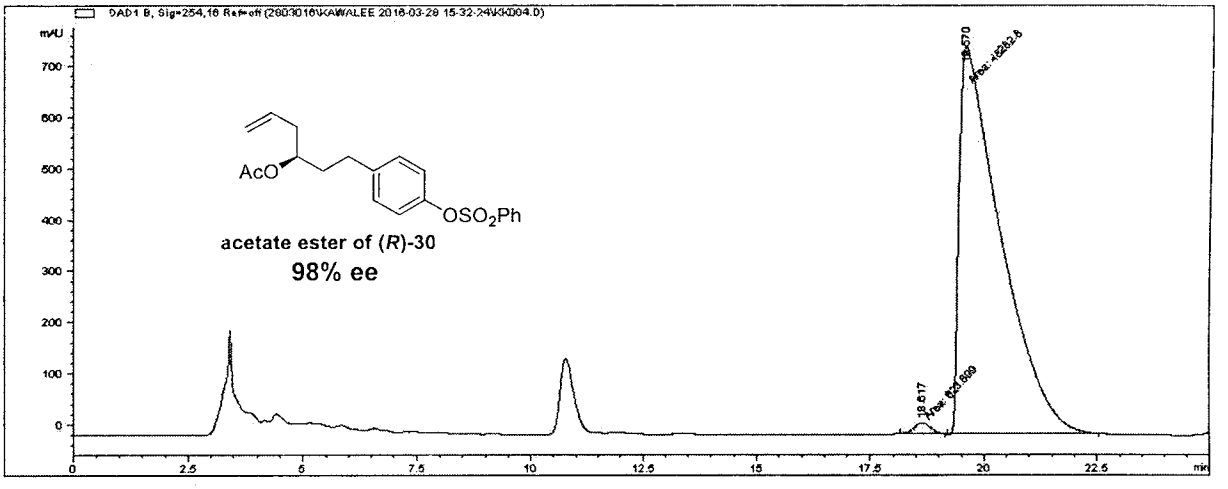


4. HPLC traces



acetate ester of *rac*-30

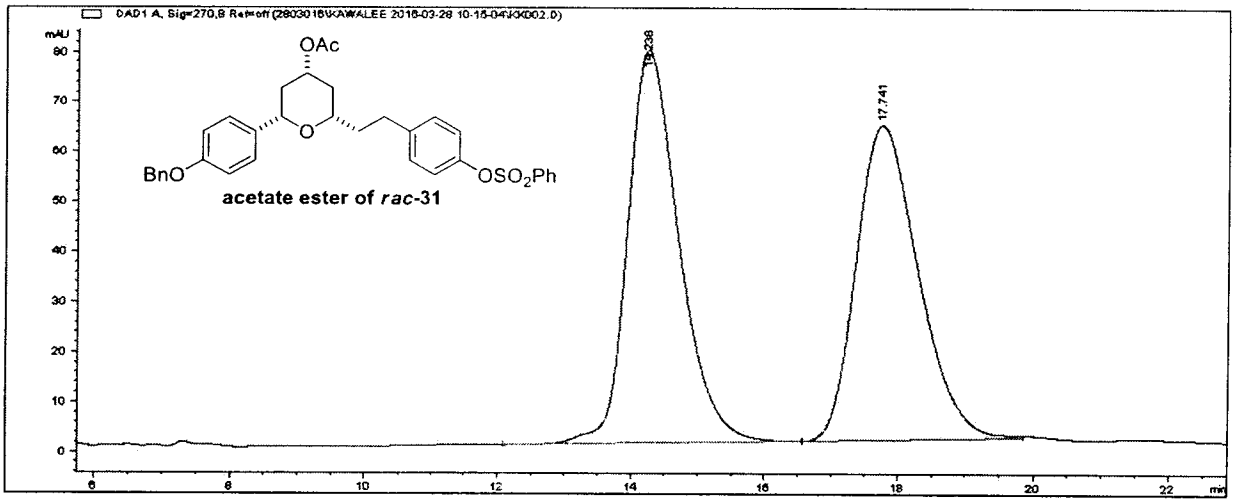
#	Time	Area	Height	Width	Area%	Symmetry
1	18.342	12376.8	309.8	0.5861	50.076	0.316
2	20.581	12339.3	252.4	0.7025	49.924	0.275



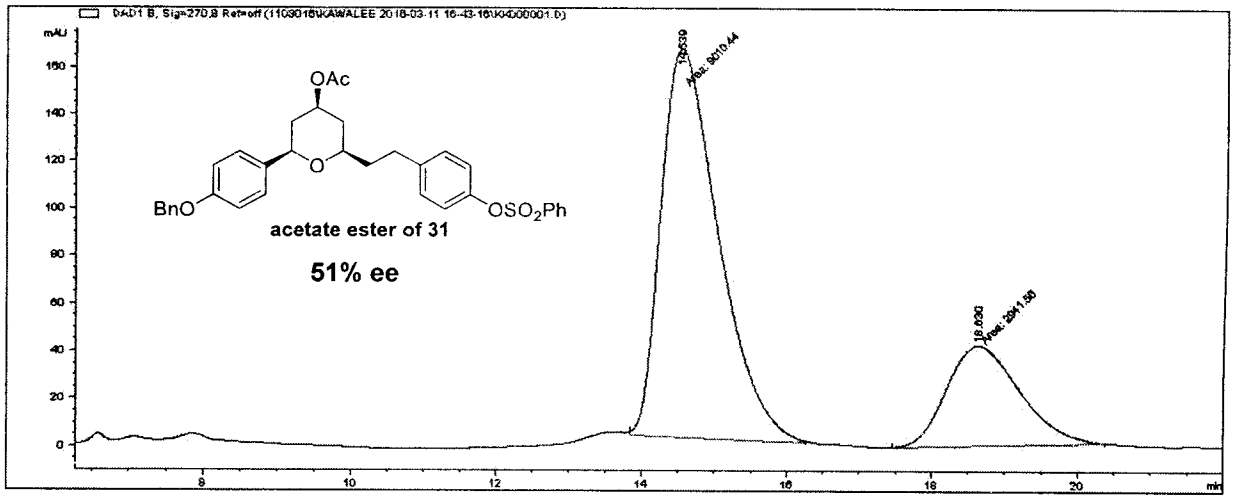
acetate ester of (*R*)-30

98% ee

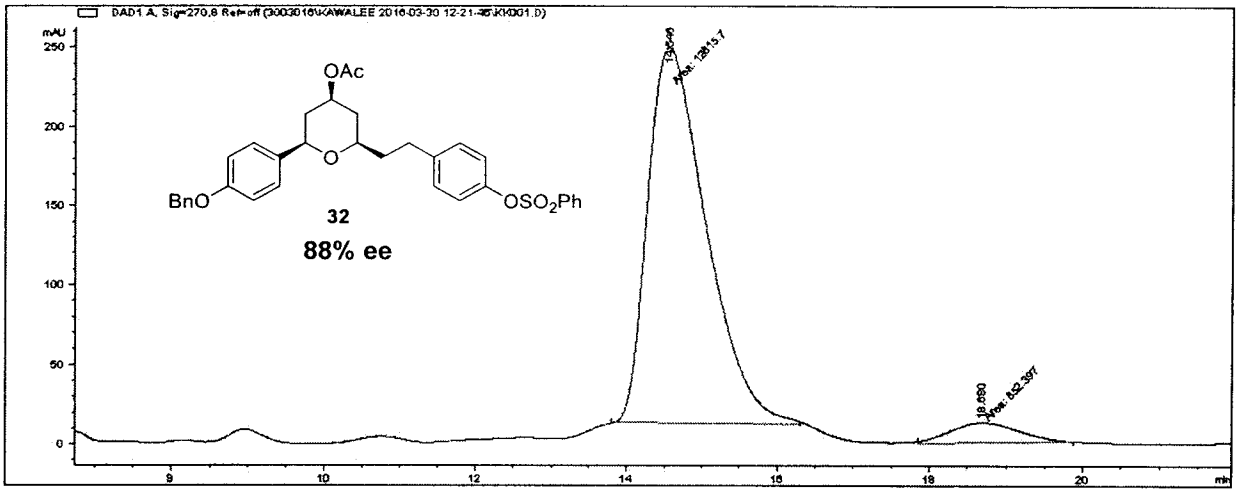
#	Time	Area	Height	Width	Area%	Symmetry
1	18.617	623.7	22.6	0.4592	1.275	0.912
2	19.57	48282.8	758.2	1.0613	98.725	0.166



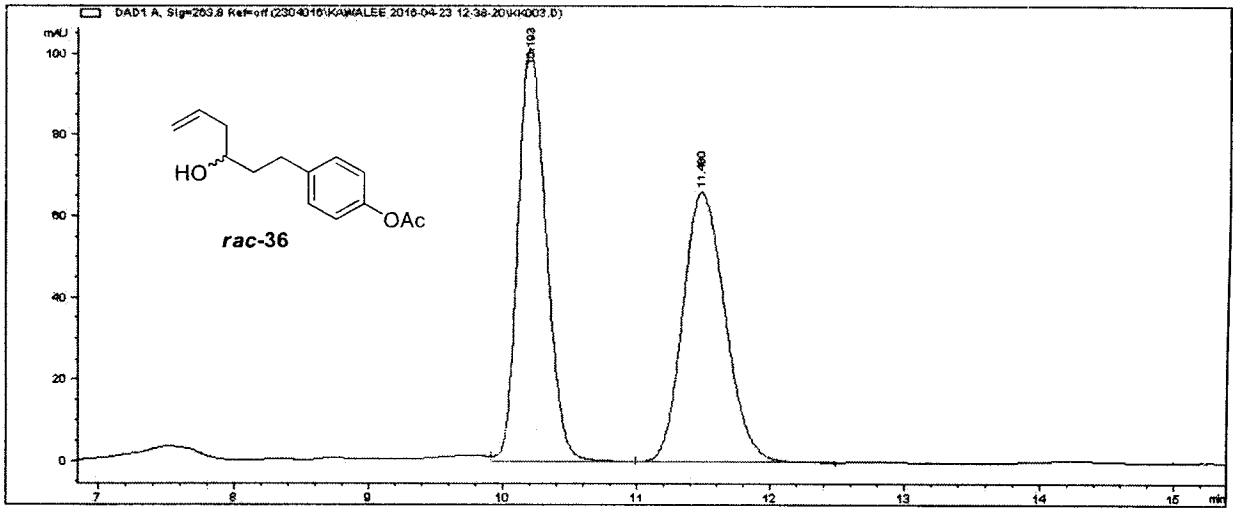
#	Time	Area	Height	Width	Area%	Symmetry
1	14.238	4213.8	78.6	0.8175	50.900	0.655
2	17.741	4064.7	63	1.0053	49.100	0.677



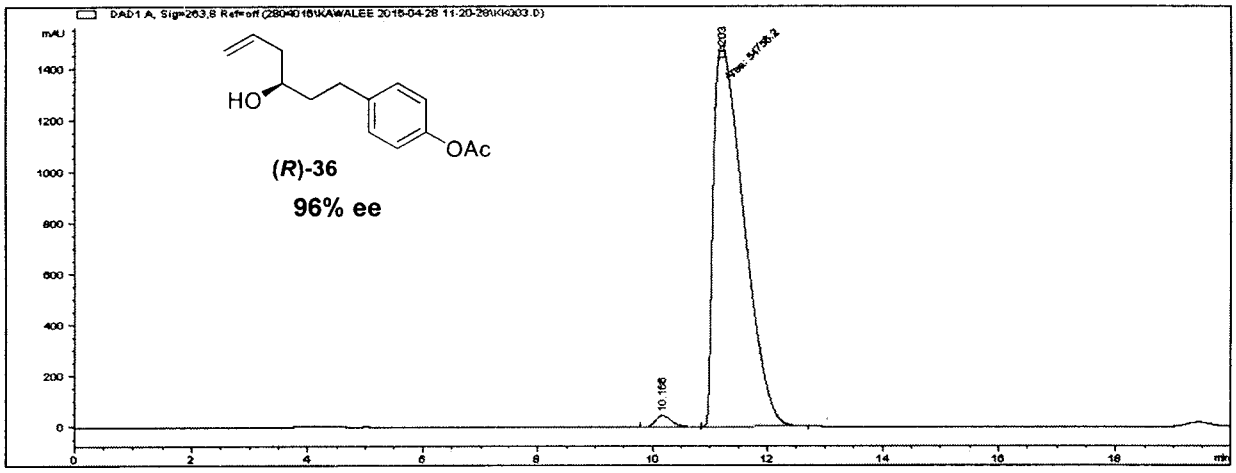
#	Time	Area	Height	Width	Area%	Symmetry
1	14.539	9010.4	164.2	0.9145	75.389	0.552
2	18.63	2941.6	42.2	1.1604	24.611	0.726



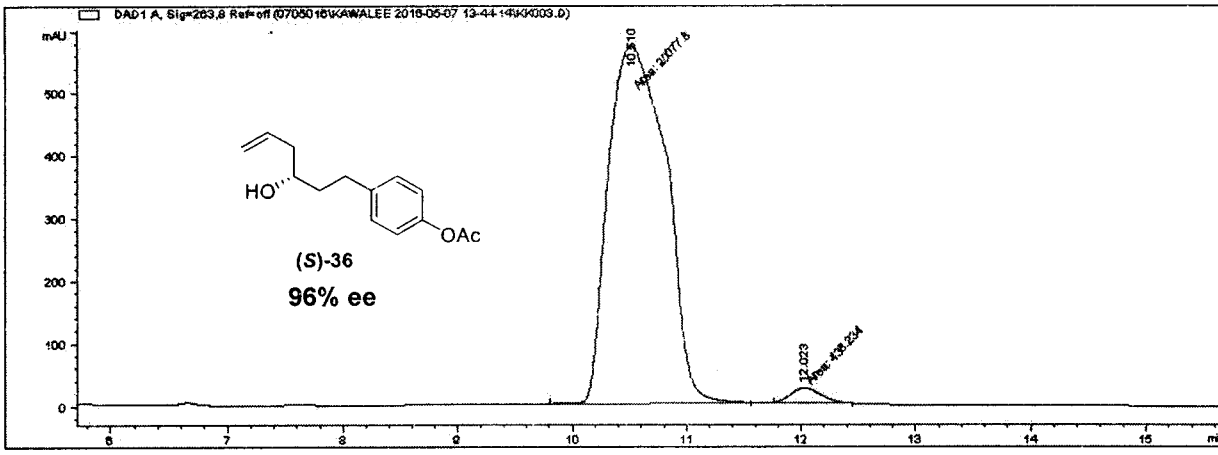
#	Time	Area	Height	Width	Area%	Symmetry
1	14.546	12815.7	237	0.9011	93.764	0.549
2	18.68	852.4	13.1	1.0818	6.236	0



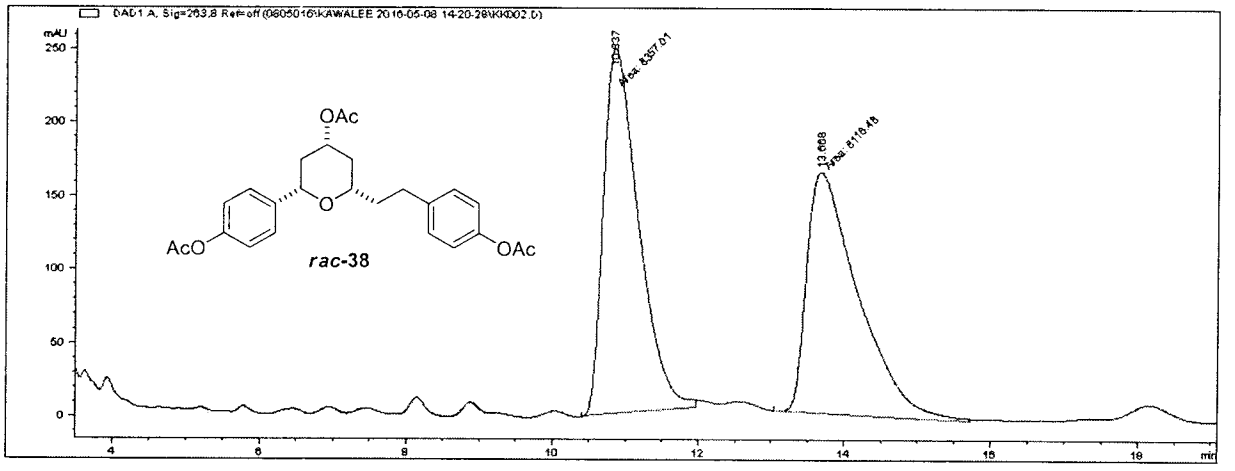
#	Time	Area	Height	Width	Area%	Symmetry
1	10.193	1494.4	101.7	0.2275	50.176	0.718
2	11.48	1483.9	66.2	0.3496	49.824	0.78



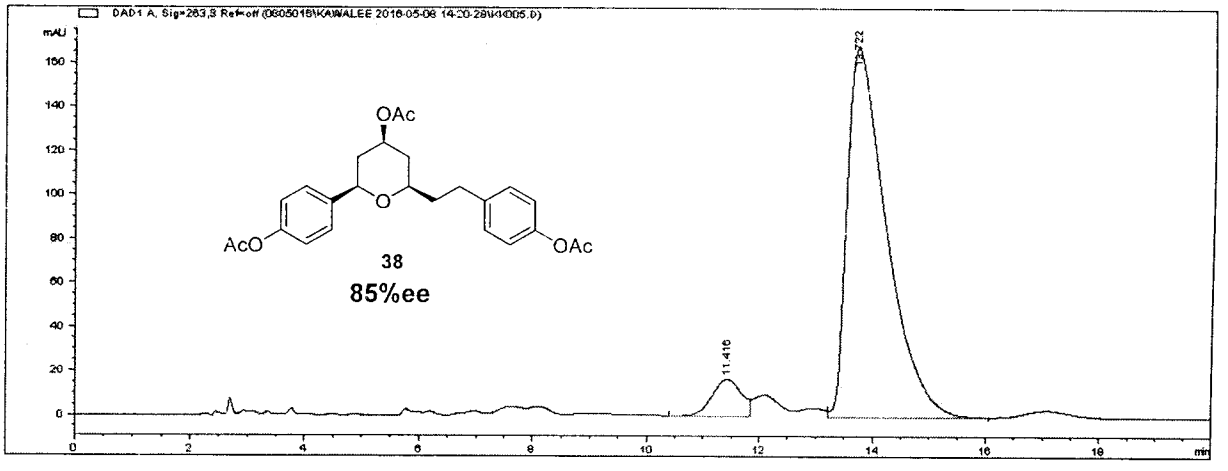
#	Time	Area	Height	Width	Area%	Symmetry
1	10.166	916.3	45.7	0.3117	1.646	0.682
2	11.203	54756.2	1490.5	0.6123	98.354	0.373



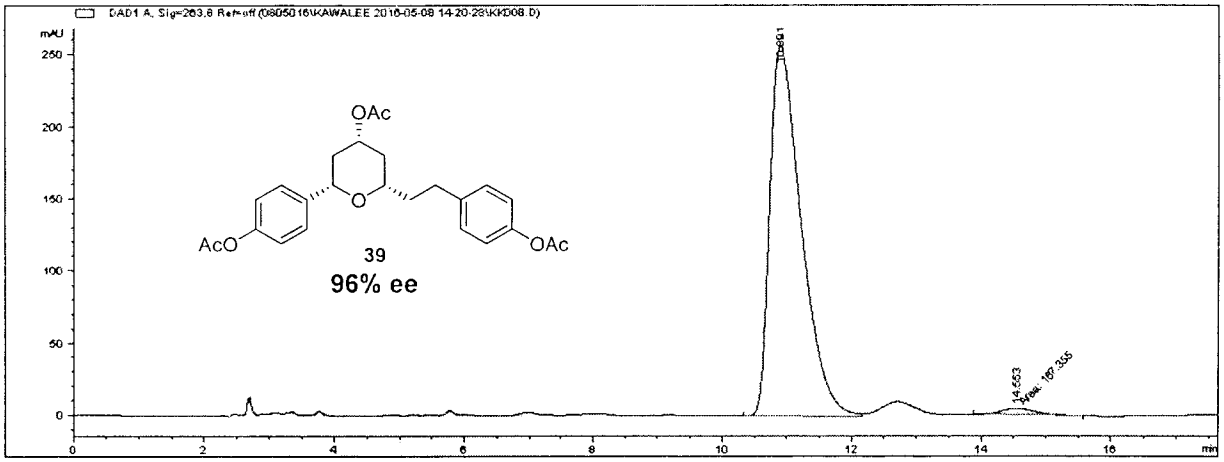
#	Time	Area	Height	Width	Area%	Symmetry
1	10.51	20077.8	573.2	0.5838	97.864	0.642
2	12.023	438.2	23.8	0.3071	2.136	0.782



#	Time	Area	Height	Width	Area%	Symmetry
1	10.837	8357	248.8	0.5598	50.730	0.489
2	13.668	8116.5	164.3	0.8231	49.270	0.368



#	Time	Area	Height	Width	Area%	Symmetry
1	11.416	658.9	17.2	0.5804	7.499	1.089
2	13.722	8128.4	168	0.7165	92.501	0.365



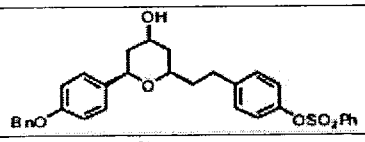
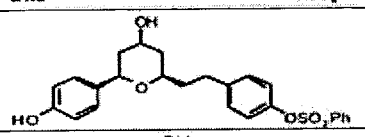
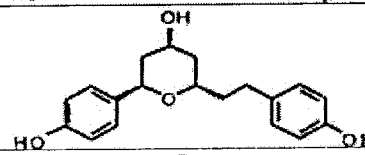
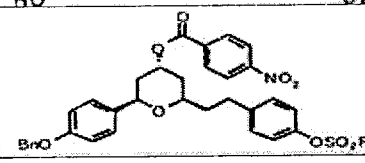
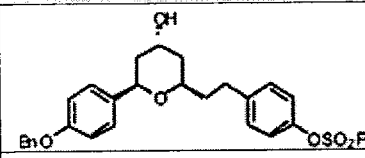
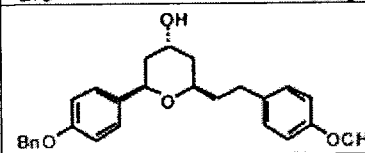
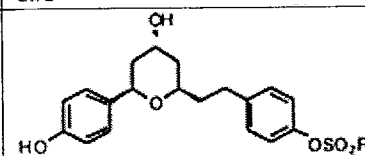
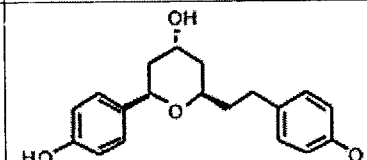
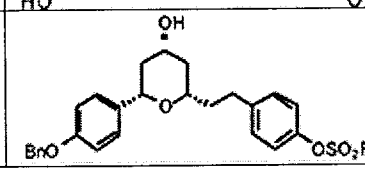
#	Time	Area	Height	Width	Area%	Symmetry
1	10.891	8736.1	257.7	0.5156	98.120	0.476
2	14.553	167.4	4.3	0.6504	1.880	0.748

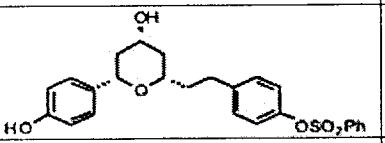
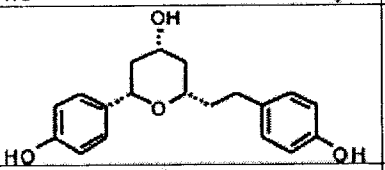
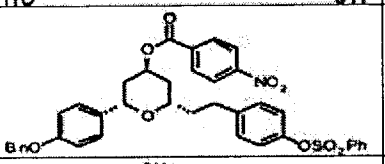
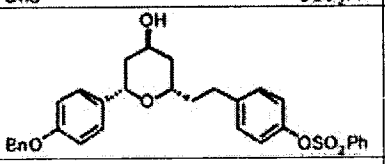
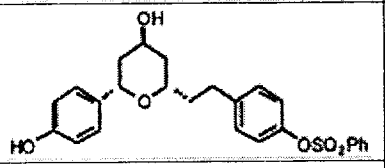
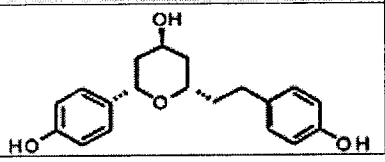
5. References

1. Njiojob, C. N.; Rhinehart, J. L.; Bozell, J. J.; Long, B. K. *J. Org. Chem.* **2015**, *80*, 1771−1780.
2. Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176–3183.
3. Nanda, S. *Tetrahedron Lett.* **2005**, *46*, 3661–3663.
4. Venkatesham, K.; Reddy, S. P.; Chinnababu, B.; Babu, K. S.*Helv. Chim.Acta.* **2015**, *98*, 1307–1314.
5. Chinnababu, B.; Reddy, S. P.; Rao, C. B.; Rajesh, K.; Venkateswarlu, Y.*Helv. Chim.Acta.* **2010**, *93*, 1960–1966.
6. Frost, C. G.; Hartley, B. C. *J. Org. Chem.* **2009**, *74*, 3599–3602.
7. Cons, B. D.; Bunt, A. J.; Bailey, C. D.; Willis, C. L. *Org. Lett.* **2013**, *15*, 2046–2049.
8. Álvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, 62, 9641–9649.
9. Szostak, M.; Spain, M.; Procter, D. J. *Org. Lett.* **2012**, *14*, 840–843.

2. ผลการวิจัยส่วนที่ยังไม่ได้ตีพิมพ์

Table 1. Antidiabetic activity via protective action against INS-1 832/13 pancreatic β-cells and cytotoxic activity against human colorectal adenocarcinoma (HT-29) cell line of synthetic diarylheptanoids **1-4** and some synthetic intermediates

Entry	Compound	Anti-diabetes	Cytotoxic activity against HT-29	
		INS-1 cells protection (protection rate at 20 μM)	% cell viability	% cytotoxicity
1		60%	90.95	9.05
2		177%	30.32	69.98
3		71%	32.89	67.11
4		No	92.58	7.42
5		No	87.75	12.25
6		140%	31.92	68.08
7		No	63.98	36.02
8		No	70.76	29.24
9		No	99.72	0.28

Entry	Compound	Anti-diabetes	Cytotoxic activity against HT-29	
		INS-1 cells protection (protection rate at 20 μM)	% cell viability	% cytotoxicity
10		99%	24.78	75.22
11		No	20.97	79.03
12		No	112.87	-12.87
13		No	74.53	25.47
14		134%	30.13	69.87
15		No	23.57	76.43