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A Practical Preparation of Pure Enantiomers of *endo*-Bicyclo[3.3.0]oct-7-en-2-ol, Versatile Intermediate for the Synthesis of Natural Products.#

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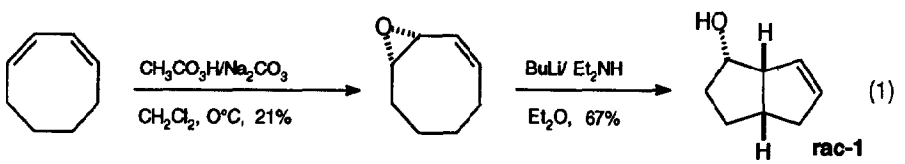
Abstract: Enantiomers of *endo*-bicyclo[3.3.0]oct-7-en-2-ol have been resolved by an efficient and practical procedure based on the utilisation of (2S)- and (2R)-1-(4-toluenesulphonyl)pyrrolidine-2-carboxylic acid chlorides [(2S)-NTP-Cl and (2R)-NTP-Cl], easily available from, respectively, (2S)- and (2R)-proline, as resolving agents.

Fused ring systems that offer different functionalities in each ring suitable for the stereocontrolled assembly of more complex structures have been regarded as amazingly versatile intermediates and starting materials. *endo*-Bicyclo[3.3.0]oct-7-en-2-ol (**1**) belongs to this important family of compounds. It is readily available as racemic material from 1,3-cyclooctadiene in two steps[1] (eq. 1) and has been used as an inexpensive starting material for the total and stereoselective synthesis of a number of cyclopentanoid natural products such as sarracenin,[2] specionin,[3] coriolin,[4] allamandin,[5,6] plumericin,[5,6] allamcin,[5,6] and prostacyclin analogues[7] (Scheme 1).

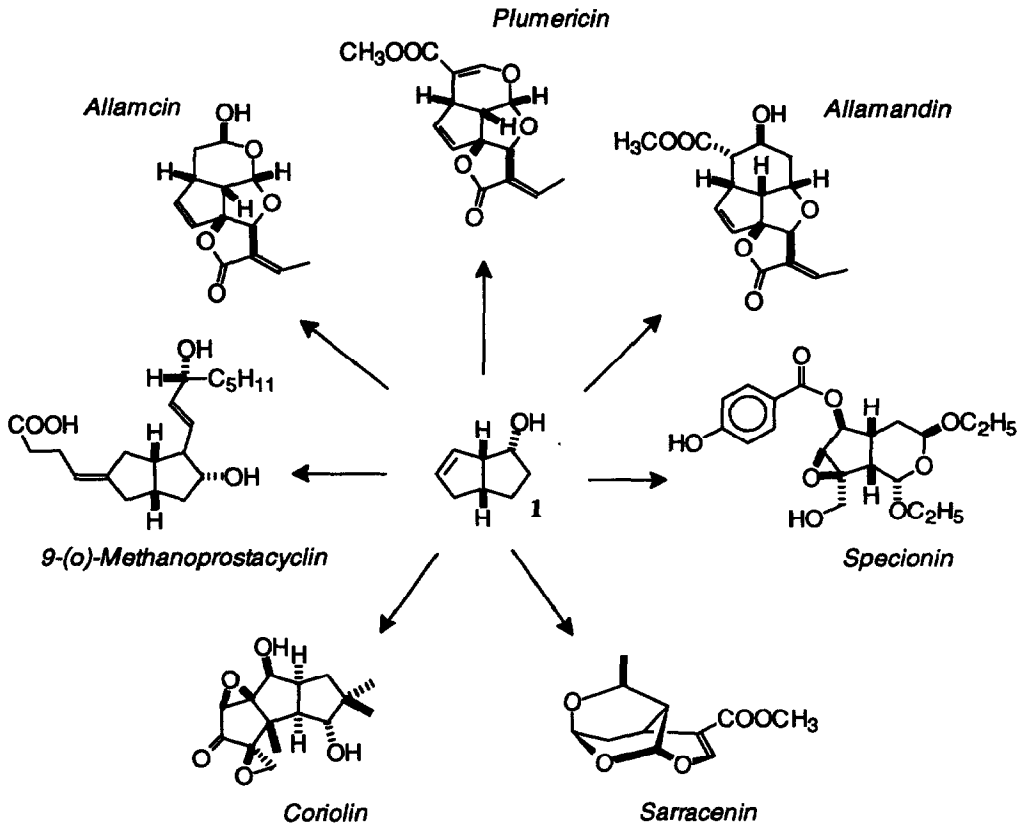


(1)

Although all these syntheses started from racemic **1** the availability of pure enantiomers of *endo*-bicyclo[3.3.0]oct-7-en-3-ol would allow the EPC synthesis[8] of those synthetic targets and the two enantiomers of compound **1** could be considered as important "chirons".[9] As a result, several attempts towards achieving this goal have been reported in the recent literature.[10-14]

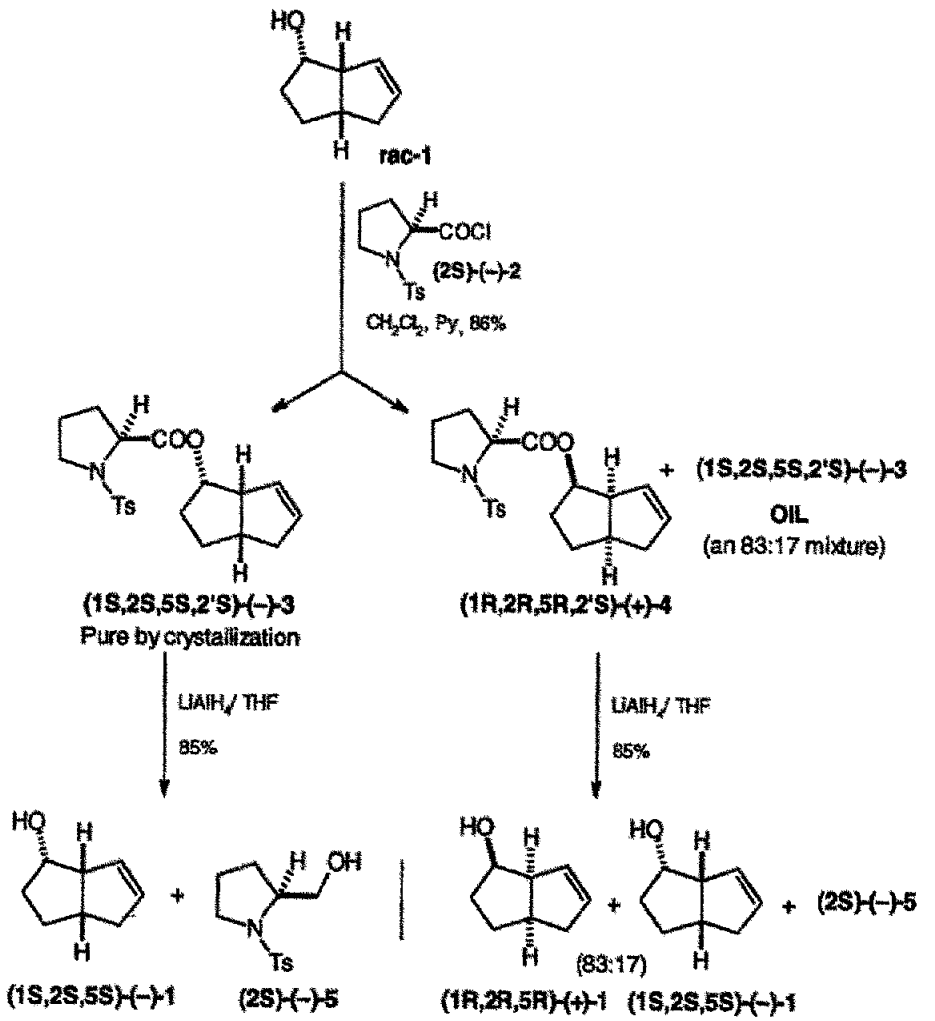
Dedicated with appreciation and best wishes to Prof. Antonino Fava.

Because of the severe limitations and drawbacks accompanying each of the previously reported resolutions of (±)-**1**, we were led to develop a practical and efficient procedure suitable for the preparation of (+)- and (–)-*endo*-bicyclo[3.3.0]oct-7-en-3-ol in gram quantities.



Scheme 1. *endo*-Bicyclo[3.3.0]oct-7-en-2-ol as a Versatile Intermediate for the Synthesis of Natural Products.

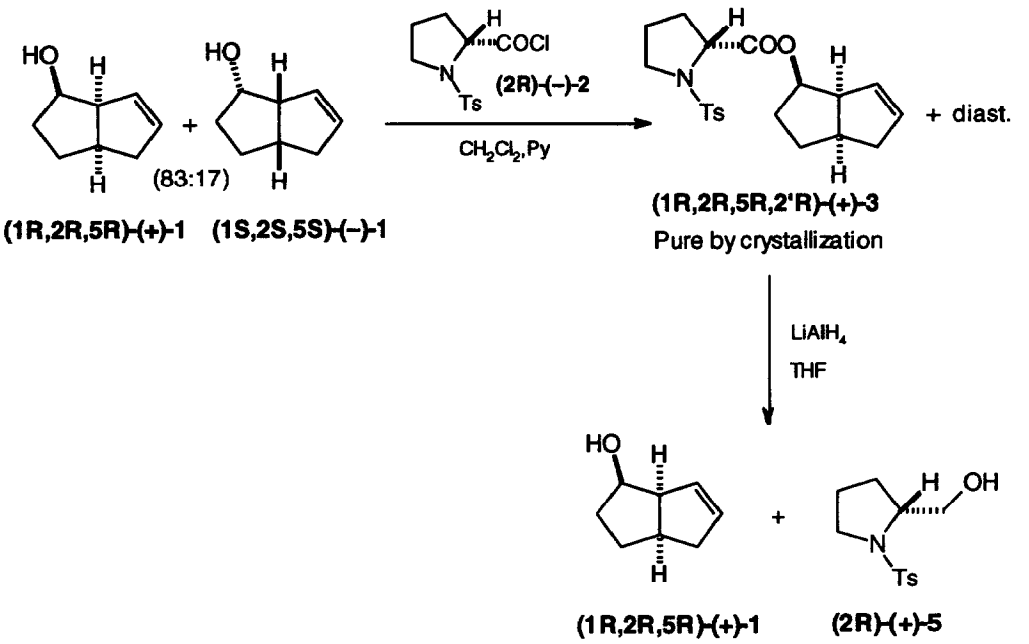
Following an approach the main guidelines of which we have described elsewhere,[15] our procedure was based on the utilisation of (2S)- and (2R)-proline as chiral substrates to obtain several differently substituted 1-benzenesulphonylpyrrolidinecarboxylic acid chlorides. The esterification of racemic **1** with these enantiomerically pure 1-substituted proline derivatives furnished the corresponding pairs of diastereoisomeric esters in high yields. This systematic approach and the crystallisation attempts performed with the thus obtained compounds allowed us to identify (2S)- and (2R)-1-(4-toluenesulphonyl)pyrrolidine-2-carboxylic acid chlorides [(2S)-NTP-Cl and (2R)-NTP-Cl, **(2S)-2** and **(2R)-2** respectively] as appropriate resolving agents for a practical and inexpensive resolution of compound **1**.[16] The access to pure enantiomers of **1** was achieved as detailed in Scheme 2 and Scheme 3.



Scheme 2. Preparation of pure (1S,2S,5S)-(–)-1 and of enriched (1R,2R,5R)-(+)-1

Pure and crystalline (–)-3 was obtained in a 70% yield by a simple crystallisation (diethyl ether/ n-hexane) of the diastereoisomeric mixture of (2S)-NTP esters obtained from the reaction of racemic 1 and (2S)-2. This diastereoisomer underwent reductive cleavage by reaction with lithium aluminium hydride in tetrahydrofuran to give enantiomerically pure (1S,2S,5S)-(–)-1 (85% yield) and 1-(4-toluenesulphonyl)prolinol [(–)-4, 87% yield].

The evaporation of the mother liquors from the crystallisation of (–)-3 afforded a viscous oil containing the other diastereoisomer as main component together with a residual 17% of (–)-3.

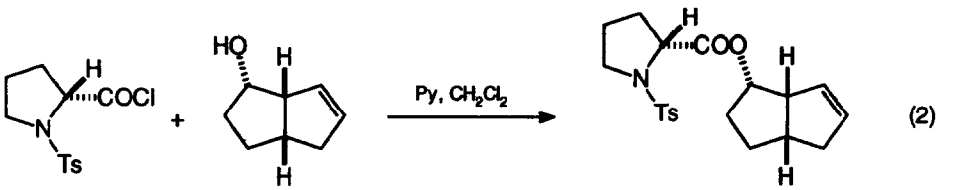


Scheme 3. Preparation of pure **(1R,2R,5R,2'R)-(+)-3** and of **(1R,2R,5R)-(+)-1**

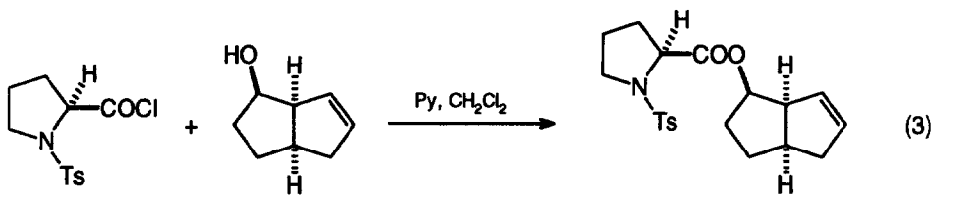
This enriched mixture was treated with $LiAlH_4$ in THF and gave **(+)-1** (ee=91%) in 90% yield and **(–)-5**. Enantiomerically pure **(+)-3** was obtained by reaction of the enriched **(+)-1** with an equimolar amount of (2R)-(+)-NTP-Cl **[(2R)-2]** and pyridine followed by crystallisation of the diastereoisomeric mixture. Again, crystalline and pure **(+)-3** was collected in 75% yield after crystallisation from ethyl ether/n-hexane and gave enantiomerically pure **(1R,2R,5R)-(+)-1** and **(+)-5** in 85% yield when reacted with $LiAlH_4$ in THF.

In order to know the physico-chemical and spectroscopic properties of the other couple of enantiomers, **(+)-4** and **(–)-4**, having a diastereoisomeric relationship with **(–)-3** and **(+)-3**, we prepared them by reacting **(–)-1** with **(2R)-(+)-2** (eq. 2), and **(+)-1** with **(2S)-(–)-2** (eq. 3).

The homochirality of **(–)-3**, **(+)-3**, **(–)-4** and **(+)-4** as well the diastereoisomeric excess of the viscous oil were rigorously established by ^1H NMR (200 MHz) spectra of the diastereoisomers and by comparison of these with the spectra registered on samples of the evaporated mother liquors. The (R)- and (S)-prolinols **(5)** could be transformed into the optically active **(R)-2** and **(S)-2** for reuse by Jones oxidation and successive reaction with oxalyl chloride in benzene.



(2R)-(+)-2 **(1S,2S,5S)-(−)-1** **(1S,2S,5S,2'R)-(−)-4**



(2S)-(−)-2 **(1R,2R,5R)-(+)-1** **(1R,2R,5R,2'S)-(+)-4**

The present method has advantages in providing a facile access to optically pure enantiomers of *endo*-bicyclo[3.3.0]oct-7-en-3-ol (**1**); it comprises practical value as well as operational simplicity. In conclusion, we suggest the sequential utilisation of N-substituted proline derivatives, such as **(2S)-2** and **(2R)-2**, as a valuable method to resolve chiral alcohols.

Experimental Section.

Melting and boiling points are uncorrected. ^{1}H NMR spectra in $CDCl_3$ solution were recorded on a Varian Gemini spectrometer operating at 200 MHz using tetramethylsilane (TMS) or $CHCl_3$ as internal standard. ^{13}C NMR were recorded in $CDCl_3$ solution at 50.30 MHz with a Varian Gemini spectrometer by the FT technique. Microanalyses were determined by using C,H,N Analyzer Model 185 from Hewlett-Packard Co.. Optical rotations were measured at 25°C on a Jasco DIP-360 polarimeter equipped with a sodium light source. Bulb-to-bulb distillation was performed using Büchi Kugelrohr apparatus, and the oven temperature is recorded as boiling point.

Preparation of 1-(4-Toluenesulphonyl)-2-pyrrolidylcarboxylates **(1S,2S,5S,2'S)-(−)-3** and **(1R,2R,5R,2'R)-(+)-3.**

A solution of (2S)-(−)-1-(4-toluenesulphonyl)prolyl chloride[17,18] [(−)-NTP-Cl, **(−)-2**, 28.81 g, 100 mmol] in dichloromethane (150 ml) and dry pyridine (10 ml, 124 mmol) was dropped into an ice-cold, stirred solution of (±)-**1**[1] (10.34 g, 83 mmol) in dichloromethane (150 ml). The mixture was stirred at room temperature for 10 h, washed with 1N hydrochloric acid (3x50 ml) and with a saturated aqueous solution of sodium bicarbonate. Finally, the dichloromethane solution was dried ($MgSO_4$). The evaporation of the solvent gave a viscous oil that was dissolved in dichloromethane, passed through a short column of silica gel and recovered (26.9 g, 86% yield). Crystallisation of this oil from *n*-hexane (200 ml) with few millilitres of diethyl ether afforded white crystals of **(1S,2S,5S,2'S)-(−)-3** (11.00 g, 81% yield): mp 102-104°C; $[\alpha]_D$ -176.59 (c 1.45; chloroform); IR(KBr) ν 1746, 1622, 1350, 1159 cm^{-1}; ^{1}H NMR δ 1.30-2.20 (9H, m), 2.40 (3H, s), 2.50-2.80 (2H, m),

3.20-3.50 (3H, m), 4.30 (1H, t, J=5.8Hz), 5.15 (1H, m), 5.41 (1H, m), 5.73 (1H, m), 7.30 (2H, d, J=8.0Hz), 7.78 ppm (2H, d, J=8.0Hz); ^{13}C NMR δ 21.68, 24.79, 31.18, 31.47, 39.66, 41.52, 48.50, 54.14, 60.82, 78.62, 128.01, 128.56, 130.06, 133.01, 136.28, 143.96, 172.34 ppm.

Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.98; H, 6.71; N, 3.73. Found: C, 64.05; H, 6.78; N, 3.68.

The mother liquors of crystallisation were evaporated at reduced pressure and a crude diastereoisomeric mixture (16.00 g) was obtained as an oil, the composition of which was determined by ^{1}H NMR spectrum in deuterochloroform. A well defined and distinct multiplet at δ=5.52 ppm for one of two olefinic hydrogens reveals that the **(1R,2R,5R,2'S)-(–)-3** is the main component (83%) while the corresponding signal of (1S,2S,5S,2'S)-(+)-3 at δ=5.41 ppm indicates a residual presence (17%) of this diastereoisomer in the mixture.

The viscous oil (9.00 g, 24 mmol) was dissolved in dry tetrahydrofuran (THF, 50 ml) and slowly added to a stirred suspension of $LiAlH_4$ (1.82 g) in THF (200 ml). The reaction mixture was left under stirring at room temperature until the ester was completely disappeared (t.l.c. control, silica gel and petroleum ether/diethyl ether 1:1 as eluent). Upon completion of the reaction, the mixture was cooled at 0°C, diethyl ether (200 ml) was added and a saturated aqueous solution of NH_4Cl was dropped to destroy the hydride in excess. The organic phase was separated, washed with water (3x 30 ml), dried (Na_2SO_4) and evaporated at reduced pressure. Washings of this residue by using cold diethyl ether (3x 30 ml) allowed a rough but efficient separation of the very soluble enriched (+)-**1** from the less soluble (2S)-1-(4-toluenesulphonyl)pyrrolydil-2-methyl alcohol [**(2S)-(–)-5**]. This latter was collected as a white solid and purified by crystallisation: mp 90-91°C from Et_2O; $[\alpha]_D$ -91.80 (c 1.65; methanol); lit.[16,17]mp 88-89°C from Et_2O; $[\alpha]_D$ -92.0 (c 1.00; chloroform). Enriched **(–)-1** was obtained chemically pure by flash column chromatography,[19] with petrol ether / diethyl ether 7:3 as eluent. distillation: bp_{30mbar}150-165°C. The purified enriched **(–)-1** (2.80 g, 22 mmol) was treated with (2R)-(+)-NTP-chloride [**(2R)-(+)-2**, 6.32 g, 22 mmol] according to the just described procedure used for racemic **1**. The work-up of the reaction mixture and crystallisation gave **(1R,2R,5R,2'R)-(+)-3** (5.30 g, 77% yield): mp 102-103°C; $[\alpha]_D$ +177.45 (c 1.46; chloroform); spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR) are identical with those of **(1S,2S,5S,2'S)-(–)-3**.

Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.98; H, 6.71; N, 3.73. Found: C, 68.85; H, 6.79; N, 3.77.

Reductive Cleavage of Esters **(1S,2S,5S,2'S)-(–)-3** *and* **(1R,2R,5R,2'R)-(+)-3**. *Preparation of enantiomerically pure* **(1S,2S,5S)-(–)** ***endo-bicyclo[3.3.0]oct-7-en-3-ol*** **[1S,2S,5S)-(–)-1]** *and* **(1R,2R,5R)-(+)-*endo-bicyclo[3.3.0]oct-7-en-3-ol*** **[(1R,2R,5R)-(+)-1].**

Ester **(–)-3** (9.00 g, 24 mmol) was treated with $LiAlH_4$ (1.82 g) in dry THF (150 ml) according to the procedure described before to obtain the enriched **(–)-1**. The residue was washed with cold diethyl ether (3x20 ml) to separate **(2S)-(–)-4** as a white solid: mp 90-91°C from Et_2O; $[\alpha]_D$ -90.10 (c 1.68; methanol). The ethereal solution was evaporated and the residue was purified by distillation: bp_{30mbar} 160-165°C. Enantiomerically pure **(1S,2S,5S)-(–)-1** was obtained as an oil (2.53 g, 85% yield): $[\alpha]_D$ -139.14 (c 1.15; chloroform) [lit.[10] $[\alpha]_D$ -124 (c 6.00; chloroform); ^{1}H NMR δ 1.21-2.20(m, 6H), 2.57-2.80 (m, 2H), 3.25 (m, 1H, C1-H), 4.22 (m, 1H, C2-H), 5.62 (m, 1H, C7-H), 5.85 ppm (m, 1H, C8-H);^{13}C NMR δ 31.50, 35.25, 40.01, 42.13, 56.39, 75.32, 128.57, 135.04 ppm.

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.45; H, 9.78.

The treatment of ester **(+)-3**, performed under the same reaction conditions described for the enantiomer **(–)-3** and the successive work-up, allowed the preparation of the enantiomerically pure **(1R,2R,5R)-(+)-1** in 85 %

yield: $[\alpha]_D$+138.26°(c 1.14; chloroform). All the spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR) are in perfect agreement with those reported for compound **(–)-1**.
Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.48; H, 9.83.

Preparation of ***(1S,2S,5S,2'R)-(–)-endo-Bicyclo[3.3.0]oct-7-en-3-ol 1-(4-Toluenesulphonyl)-2-pyrrolidylcarboxylates*** **[(1S,2S,5S,2'R)-(–)-4]** *and of* ***(1R,2R,5R,2'S)-(+)-endo-Bicyclo[3.3.0]oct-7-en-3-ol 1-(4-Toluenesulphonyl)-2-pyrrolidylcarboxylates*** **[(1R,2R,5R,2'S)-(+)-4]**.
Compound **(1S,2S,5S)-(–)-1** (0.50 g, 4.03 mmol) and (2R)-(+)-NTP-Cl **[(+)-2**, 1.50 g, 5.22 mmol] were treated in dichloromethane and dry pyridine as described before for the conversion of racemic **1**. Work-up of the reaction mixture gave **(1S,2S,5S,2'R)-(–)-4** (1.36 g, 90% yield) as a low melting solid: mp 36-38°C; $[\alpha]_D$ -28.43 (c 1.44; chloroform); IR(KBr) ν 1726, 1598, 1339, 1166 cm^{-1} ^{1}H NMR δ 1.25-2.20 (m, 9H), 2.40 (s, 3H), 2.50-2.80 (m, 2H), 3.20-3.55 (m, 3H), 4.28 (t, 1H, J=5.8 Hz), 5.10 (m, 1H), 5.50 (m, 1H), 5.75 (m, 1H), 7.30 (d, 2H, J= 8.0 Hz), 7.78 ppm (d, 2H, J= 8.0 Hz);^{13}C NMR δ 21.69, 24.76, 31.18, 31.36, 39.70, 41.56, 48.58, 54.14, 60.94, 78.63, 127.97, 128.76, 130.10, 132.94, 136.27, 143.97, 172.47 ppm.
Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.98; H, 6.71; N, 3.73. Found: C, 64.06; H, 6.63; N, 3.81.
The esterification of **(1R,2R,5R)-(+)-1** (0.50 g, 4.03 mmol) with (2S)-(–)-NTP-Cl **[(–)-2**, 1.50 g, 5.22 mmol] gave **(1R,2R,5R,2'S)-(+)-4** (1.40 g, 93% yield): mp 36-38°C; $[\alpha]_D$+28.43 (c 1.44; chloroform). Its IR, ^{1}H NMR, and ^{13}C NMR spectra were identical with those of **(1S,2S,5S,2'R)-(–)-4**.
Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.98; H, 6.71; N, 3.73. Found: C, 64.08; H, 6.78; N, 3.79.

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