Asymmetric Synthesis of a D-ring synthon for Strigol Analogues and its Application to the Synthesis of all Four Stereoisomers of Germination Stimulant GR7

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Abstract: A novel asymmetric synthesis of the strigol analogue GR7 has been developed. The olefinic double bond of the butenolide D-ring was protected as a Diels-Alder adduct with cyclopentadiene. The thus obtained tricyclic compound was resolved and transformed into a suitable D-ring synthon. The coupling reaction with the GR7-precursor, hydroxymethylenolactone proceeded with complete stereocontrol. Cycloreversion under relatively mild conditions gave GR7 in an optically pure form.

Introduction

Parasitic weeds of the genera Striga, Alectra, and Orobanche cause severe damage to graminaceous and leguminous crops in tropical and semitropical areas of the eastern hemisphere. Germination of the seeds of these parasitic weeds is triggered by a chemical species exuded by roots of a suitable host plant. (+)-Strigol 1 was the first isolated naturally occurring germination stimulant from the root exudate of the false host cotton (Gossypium hirsutum L.) and its structure was elucidated by Cook. The absolute configuration was unambiguously determined by Brooks several years later. Only very recently strigol has also been found in the root exudates of Striga host plants.

1, (+)-strigol  
2, sorgolactone  
3, alectrol  
5, GR24  
4, GR7
Some structures closely related to strigol (sorgolactone 2 and alectrol 3) have been proposed to occur in the root exudates of *Sorghum bicolor* and *Vigna unguiculata*, which are hosts for *Striga* and *Alectra* species, respectively. An attractive way for parasitic weed control is to use these germinating agents as herbicides in the absence of suitable host plants (concept of suicidal germination). However, these naturally occurring germination stimulants are not suitable for this purpose, due to their complicated structures and to their intrinsic lability in alkaline soils. Inspired by the work of Johnson and Pepperman, we have synthesized several structurally simpler analogues of (+)-strigol with the aim to overcome these problems and to retain the biological activity. Highly potent strigol analogues are compounds 4 and 5, commonly known as GR7 and GR24, respectively.

Thus far, relatively scarce attention has been paid to the influence of the stereochemistry on the activity of strigol analogues. This is mainly due to the fact that no general method is known toward the synthesis of homochiral strigol analogues. Optically active strigol has been obtained by resolution of racemic strigol, resolution of the ABC-part of strigol, and by asymmetric synthesis (chiral pool approach). Recently, we synthesized all four stereoisomers of GR7 starting from commercially available enantiopure Corey's lactone, and of GR24, which were synthesized by chromatographic resolution of the tricyclic ABC-moiety on cellulose triacetate. From appropriate bioassays we concluded that the stereochemistry at C-2' is more important, with respect to germination stimulant activity, than the configuration at the other stereogenic centers. This finding was confirmed by Welzel in a study in which the seeds of *Orobanche crenata* were treated with all stereoisomers of strigol.

Thus far, homochiral strigol and some analogues have been obtained starting from an enantiopure ABC precursor I. We present a novel, versatile synthetic route to homochiral strigol analogues with complete stereocontrol at C-2'.

Results and discussion

In order to achieve stereocontrol at C-2' it is essential to protect the double bond in 6. While our investigations were in progress, Welzel published a strategy, involving a phenylthio group as double bond protection and to control stereoselective bond formation at C-2'. However, this method is rather laborious and needs considerable improvement. Conceptually, our approach is outlined in figure 1.
Four stereoisomers of GR7 5049

Protection of the double bond of the D-ring as a Diels-Alder adduct gives racemic PD*, which is subsequently resolved by an enantiopure auxiliary Q. A suitable racemic ABC-synthon of a strigol analogue is coupled to the thus obtained enantiomers of PD. Separation of the diastereomers, followed by removal of the auxiliary P affords all possible stereoisomers of the strigol analogue.

As is depicted in scheme 2 we started with the Diels-Alder adduct of citraconic anhydride and cyclopentadiene 7, which we used already in the synthesis of the racemic butenolide 6.24

Partial reduction employing Li(O-t-Bu)3AlH gave hydroxy lactone rac. 8.25 At this stage it is appropriate to perform the resolution. Treatment of rac. 8 with l-menthol in the presence of a catalytic amount of p-TsOH under azeotropic conditions for 18 h gave a mixture of exo 5R-, exo 5S-, endo 5R-, and endo 5S-l-larythroxy lactones in a ratio of 44:44:6:6. If the reaction was stopped after 4 h the product distribution of 9(a+b):9(c+d):8 amounted to 52:24:22, suggesting that the initially formed isomers 9(c+d) (kinetic products) epimerize under the reaction conditions to the thermodynamically isomers 9(a+b). The product distribution could unambiguously be determined by an 1H-NMR analysis. The exolendo assignments were made on the basis of chemical shifts and coupling constants. The acetal proton H5 of the endo isomers 9(c+d) exhibited a doublet (3J = 6.7 Hz) at ca. 0.7 ppm lower field as compared to the corresponding exo isomers 9(a+b) (3J = 1.2 Hz). The coupling constants were verified by MM-2 calculations and are in complete agreement with those reported for similar systems26. Diastereoisomer 9a has already been synthesized by Feringa27 via a different route, although no analytical data were reported. Without any further purification diastereomer 9a could be crystallized selectively from the crude reaction mixture (from n-hexane, 100% d.e., 28% yield). It was not possible to obtain more of this diastereoisomer in a pure form by repeated crystallization of the
residue. Therefore, the starting hydroxy lactone 8 (enantiomerically enriched) was recovered and treated as is outlined in scheme 3.

The residue, containing mainly 9b and smaller amounts of 9a, 9c, and 9d was hydrolyzed in 80% TFA to give 8b (enantiopurity Y 69%), which could readily be purified by a quick filtration on silica. Subsequent treatment with d-menthol under azeotropic conditions gave 10a as the main stereoisomer, which is the enantiomer of 9a and could thus again readily be crystallized from the crude mixture (24% yield, 100% d.e.). This procedure is easy to perform and can be accomplished without significant loss of material.

With both enantiopure menthylxy lactones 9a and 10a in hand, these were transformed into suitable synthons for coupling reactions with strigol precursors of type I (scheme 1). The chiral auxiliary l-menthol was readily removed by hydrolysis in 80% TFA leading to enantiopure hydroxy lactone 8a (scheme 4). In order to transform the hydroxyl function into a halogen atom, some test experiments were performed starting from rac. 8. Bromination under S_{N}2 conditions (CBr_{4}, PPh_{3}, Et_{3}N) of racemic 8 gave after 18h a mixture of two isomeric products (exo-11 and endo-12) in a ratio 1:1. Careful TLC analysis revealed that initially endo-12 was formed as the kinetic product, which slowly epimerized to exo-11. Unfortunately, exo-11 and endo-12 are unstable and, in addition, they did not give satisfactory results in the coupling reactions. Therefore, the
synthesis of the corresponding chloro lactone 13a was undertaken. Treatment of enantiopure 8a with excess SOCl2 in the presence of 1 equivalent of pyridine smoothly gave both epimers exo-13a and endo-14a in a ratio of 6:1 in almost quantitative yield. Again, endolexo assignments were made on the basis of coupling constant (1.0 vs. 7.0 Hz) and the difference in chemical shift. By column chromatography enantiopure exo-13a was obtained.

Scheme 4

The coupling reaction of exo-13a with the GR7 precursor, rac. hydroxymethylenolactone 1519, gave two diastereomeric adducts 16a and 16b in the expected ratio of 1:1 with complete exo selectivity (scheme 5). It should be noted that the R/S-assignment in 13a and 16 has changed, due to the priority rules. Starting from exo-13b, the corresponding enantiomers 16c and 16d could be synthesized in the same manner.

Finally, the cycloreversion step was investigated. In the literature only three reports are known in which a system of type IV, having an alkyl substituent at C-2, is subjected to a retro Diels-Alder reaction (scheme 6):

Scheme 6

The reaction conditions are either heating at 240°C-285°C for several days in a sealed tube28 or thermolysis under flash vacuum conditions (short contact time) at 300°C-330°C29 or at 500°C (X = H)24.

In order to prevent epimerization at C-2 in 4 during the thermolysis, the reaction should be carried out under mild conditions. This could be accomplished by heating the Diels-Alder adducts 16a, 16b and 16c, 16d in o-dichlorobenzene at 180°C for 15h (scheme 5). Under these conditions the cycloreversion occurred without significant epimerization in yields of 50-64%. In this manner the 4 diastereomers of GR7, viz 4a, 4b, 4c & 4d were obtained in enantiopure form. The physical data are in complete agreement with those previously reported19. It is noteworthy that heating of the l-menthoxy lactone 9a under the same conditions led to the corresponding butenolide, which was completely epimerized at C-5.

In conclusion, a highly efficient route with excellent stereocontrol is developed for the synthesis of all stereoisomers of the synthetic strigol analogue GR7. This method can easily be extended to the asymmetric synthesis of other strigol analogues. This topic, along with the optimalization of the cycloreversion step is under active investigation in our laboratory.
Scheme 5

exo 13a (5S) + rac. 15 → (a) 72% 16a 3a(R), 6a(R), 5(R) 50-64% Me
Or 16b 3a(S), 6a(S), 5(R)
(ratio 1:1)

4a 3a(R), 6a(R), 2'(R) 4b 3a(S), 6a(S), 2'(R)

a: KOtBu, DMF, 20h, separation of diastereoisomers
b: o-dichlorobenzene, 180°C.

exo 13b (5R) + rac. 15 → (a) 78% 16c 3a(R), 6a(R), 5(S)
50-59% Me
Or 16d 3a(S), 6a(S), 5(S)
(ratio 1:1)

4c 3a(R), 6a(R), 2'(S) 4d 3a(S), 6a(S), 2'(S)
Experimental section

General remarks

100 MHz 1H-NMR spectra were recorded on a Bruker AC 100 spectrometer (Me4Si as internal standard) and 400 MHz 1H-NMR spectra were recorded on a Bruker AM-400 spectrometer (Me4Si as internal standard). All coupling constants are given as 3J in Hz, unless indicated otherwise. For mass spectra a double focussing VG7070E mass spectrometer was used. GC-MS spectra were run on a Varian Saturn 2 GC-MS ion-trap system. Separation was carried out on a fused-silica capillary column (DB-5, 30m x 0.25 mm). Helium was used as carrier gas, and electron impact (EI) was used as ionization mode.

GLC was conducted with a Hewlet-Packard HP 5890 gas chromatograph, using a capillary column (25m) of HP-1, and nitrogen (2 ml/min, 0.5 atm) as the carrier gas. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed at the Department of Micro-analysis of this laboratory.

Solvents were dried using the following methods: Dimethylformamide (DMF) P.A. was dried on 4-A molecular sieves. Dichloromethane was distilled from P2O5. Diethyl ether was distilled from NaH. Hexane was distilled from CaH2. Ethyl acetate was distilled from K2CO3. Trifluoroacetic acid (TFA) was used as an 80% (v/v) aqueous solution. All other solvents were of analytical grade. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F254 plates (0.25 mm) using the eluents indicated. Spots were visualized with UV or using a molybdate spray. "Flash" chromatography was carried out at a pressure of ca. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was carried out, using Merck Kieselgel 60.

5(R)-[2(S)-Isopropyl-5(R)-methyl-(R)-cyclohexyloxyl-2(S).methyl-4-oxa-endo tricyclo[5.2.1.02,6]dec.8-en-3-one (9a) and its enantiomer (10a)

Rac. exo-hydroxy tricyclic lactone 825 (7.60 g, 42.2 mmol) and /-menthol (7.90 g, 50.7 mmol) were dissolved in benzene (125 mL) containing 0.05 eq. p-TsOH (401 mg, 2.11 mmol). The mixture was heated under reflux for 18h, using a Dean-Stark trap. After evaporation of the solvent, the residue was dissolved in a mixture of saturated NaHCO3 and ethyl acetate. Extraction with ethyl acetate (2x), washing the combined organic layers with brine, and drying (MgSO4) provided crude product in quantitative yield. Based on 1H-NMR analysis the product consisted of a mixture of 4 diastereomers 9a-d in a ratio 44:44:6:6. The crude mixture was crystallized from n-hexane to give pure 9a (3.72 g, 28%) as colorless needles. Mp 131.5-132.5 °C; [Ct]D -1470 (c 0.40, CH2Cl2); 1H-NMR (CDCl3, 100 MHz): δ 0.72-1.02 (m, 12H), 1.20 (m, 3H), 1.52 (s, 3H), 1.64 (m, 3H), 2.01-2.18 (m, 2H), 2.45 (dd, J = 0.9, 4.1 Hz, 1H), 2.82 (m, 1H), 3.10 (m, 1H), 3.48 (dt, J = 4.2, 10.5 Hz, 1H), 5.02 (d, J = 0.9 Hz, 1H), 6.21 (m, 2H); GC-MS (El, m/z, rel. int. (%)): 319 (M÷+I, 1.6), 253 (1.8), 181 (100), 163 (17.4), 115 (10.3), 66 (41.3); Analysis calcd for C20H30O3: C, 75.43; H, 9.49. Found: C, 75.55; H, 9.11.

The mother liquor (9.73 g) was dissolved in 80% TFA (30 mL) and stirred for 18 h at room temperature. After evaporation of the solvent under reduced pressure the crude product was purified by chromatography (SiO2, hexane / ethyl acetate 9:1) to remove the apolar by-products /-menthol and l-menthyl trifluoroacetate. The product was then quickly eluted from the column (hexane / ethyl acetate 1:1) to give 8 as a solid (4.00 g, 73%). Without further purification 8 was treated with d-menthol under the same conditions as described for the preparation of 9a. Yield of 10a (d.e.> 98%) after crystallization from n-hexane 3.29 g, 24% (calculated from starting rac. alcohol 8). Mp 131-132.5 °C; [α]D +1480 (c 0.38, CH2Cl2); Analysis calcd for C20H30O3: C, 75.43; H, 9.49. Found: C, 75.35; H, 9.67. 1H-NMR and mass data were the same as for compound 9a.

5(R)-Hydroxy-2(S)-methyl-4-oxa-endo tricyclo[5.2.1.02,6]dec-8-en-3-one (8a)

Enantiopure l-mentholoxy lactone 9a (3.65 g, 11.5 mmol) was dissolved in 80% (v/v) TFA (50 mL) and stirred for 18 h at room temperature. After evaporation of the solvent under reduced pressure the crude product was purified by chromatography (SiO2, hexane / ethyl acetate 9:1) to remove the apolar by-products l-methyl and l-methyl trifluoroacetate. The product was then quickly eluted from the column (hexane / ethyl acetate 1:1) to give 8a as a solid (1.99 g, 97%), which was sufficiently pure for further reactions. An analytical sample was obtained by recrystallization from hexane/ethyl acetate. Mp 180-182 °C; [α]D +21.70 (c 0.42, CH2Cl2); 1H-NMR (CDCl3, 100 MHz): δ 1.55 (s, 3H), 1.66 (m, 2H), 2.52 (dd, J = 1.2, 4.1 Hz, 1H),
5(S)-Hydroxy-2(R)-methyl-4-oxa-endo tricyclo[5.2.1.02,6]dec-8-en-3-one (8b)
This compound was prepared from d-menthyloxy lactone 10a (3.12 g, 9.80 mmol) in the same way as described for its enantiomer 8a. Yield 1.71 g, 97%. Mp 173-175°C; [α]D -21-80 (c 0.40, CH2C12); Analysis calcd for C10H12O3: C, 66.65; H, 6.71. Found: C, 66.41; H, 6.57. 1H-NMR, and mass data were the same as for compound 8a.

5(S)-Chloro-2(S)-methyl-4-oxa-endo tricyclo[5.2.1.02,6]dec-8-en-3-one (13a) and its 5(R) epimer (14a)
Enantiopure 5(R)-hydroxy lactone 8a (1.90 g, 10.6 mmol) was dissolved in SOCl2 (10 mL) in the presence of pyridine (0.92 g, 11.6 mmol) at 0°C. The solution was allowed to warm up to room temperature and stirred for 1 h. Excess SOCl2 was removed by evaporation under reduced pressure. The pyridinium.HC1 salt was removed by filtration and the filtrate was concentrated to dryness. Purification by flash chromatography (hexane / ethyl acetate 9:1) gave exo-5(S)-chloro lactone 13a (1.59 g, 78%) as a solid and endo-5(R)-chloro lactone 14a (272 mg, 13%), which solidified on standing. Analytical samples of 13a and 14a were obtained by recrystallization from n-hexane.

13a Mp 97-99°C; [α]D -6.70 (c 0.64, CH2C12); 1H-NMR (CDCl3, 100 MHz): δ 1.64 (s, 3H), 1.69 (m, 2H), 2.90 (m, 1H), 3.00 (dd, J = 1.0, 4.2 Hz, 1H), 3.24 (m, 1H), 5.70 (d, J = 1.0 Hz, 1H), 6.23 (m, 2H); GC-MS (EI, m/z, rel. int. (%)): 201/199 (M++I, 2.3), 163 (7.5), 97 (6.0), 91 (15.2), 66 (100); Analysis calcd for C10H11O2Cl: C, 60.46; H, 5.58. Found: C, 60.48; H, 5.57.

14a Mp 67-68°C; [α]D +6.70 (c 0.4, CH2C12); 1H-NMR (CDCl3, 100 MHz): δ 1.54 (s, 3H), 1.71 (m, 2H), 2.86 (m, 1H), 2.97 (dd, J = 3.9, 7.0 Hz, 1H), 3.20 (m, 1H), 6.23 (d, J = 7.0 Hz, 1H), 6.24 (m, 1H), 6.44 (m, 1H); Analysis calcd for C10H11O2Cl: C, 60.46; H, 5.58. Found: C, 60.40; H, 5.64.

2(S)-Methyl-5(R)-(2-x-3a(R)6a(R)-dihydro-6H-cyclopenta[b]furan-3-ylidenemeth-xy)-4-xa-end
tricyclo[5.2.1.02,6]dec-8-en-3-one (16a) and its 3a(S),6a(S) diastereomer (16b)
Potassium tert-butoxide (139 mg, 1.24 mmol) was added to a solution of racemic hydroxymethylenolactone 15 (180 mg, 1.18 mmol) in dry DMF (6 mL) with stirring at room temperature under nitrogen. To this solution was gradually added exo-5(S)-chloro lactone 13a (213 mg, 1.07 mmol) in dry DMF (4 mL) at room temperature. After 22 h of stirring the reaction mixture was quenched with acetic acid (0.5 mL). DMF was removed in vacuo and the residue was dissolved in a mixture of water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated NaHCO3, and water, dried (MgSO4), filtered, and concentrated. The crude product was purified using flash chromatography (SiO2, hexane / ethyl acetate 3:1) to afford two diastereomeric products. The fast moving diastereomer 16a (114 mg, 34%) was obtained as a white solid, and crystallization from hexane/ ethyl acetate afforded analytically pure 16a. The slow moving diastereomer 16b (128 mg, 38%) was obtained as a white solid, which gave an analytically pure sample after crystallization from hexane/ ethyl acetate.

16a Mp 180-181.5°C; [α]D +175° (c 0.12, CHCl3); 1H-NMR (CDCl3, 400 MHz): δ 1.58 (s, 3H), 1.73 (m, 2H), 2.69 (dm, J = 18.6 Hz, 1H), 2.72 (d, J = 4.2 Hz, 1H), 2.80 (dm, J = 18.6 Hz, 1H), 2.90 (m, 1H), 3.23 (m, 1H), 4.07 (m, 1H), 5.11 (dt, J = 2.5, 6.4 Hz, 1H), 5.21 (br s, 1H), 5.64 (m, 1H), 5.75 (m, 1H), 6.21 (dd, J = 2.9, 5.7 Hz, 1H), 6.30 (dd, J = 3.0, 5.7 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H); MS (EI, m/z, rel. int. (%)): 315 (M++1, 0.06), 249 (0.13), 163 (66.0), 153 (5.3), 97 (100), 91 (4.5), 66 (8.4); Analysis calcd for C18H18O5: C, 68.78; H, 5.77. Found: C, 68.67; H, 5.57.
Four stereoisomers of GR7

16b Mp 205-207°C; [α]D -255° (c 0.13, CHCl3); 1H-NMR (CDCl3, 400 MHz): δ 1.59 (s, 3H), 1.73 (m, 2H), 2.67 (dm, 2J = 18.5 Hz, 1H), 2.73 (d, J = 4.2 Hz, 1H), 2.80 (dm, 2J = 18.5 Hz, 1H), 2.90 (m, 1H), 3.22 (m, 1H), 4.08 (s, 1H), 5.10 (d, J = 2.9, 5.7 Hz, 1H), 6.31 (dd, J = 3.0, 5.7 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H); MS (EI, m/z, rel. int. (%)): 315 (M+1, 0.76), 249 (0.29), 163 (78.0), 153 (6.4), 97 (100), 91 (4.9), 66 (8.7); Analysis calcd for C18H18O5: C, 68.78; H, 5.77. Found: C, 68.62; H, 5.68.

2(R)-Methyl-5(S)(2α,3α)-diisopropyl-6H-cyclopenta[b]furan-3-ylidenemethoxy)-4-oxa-enododec-8-ene-3-one (16c) and its 3α(S),6α(S) diastereomer (16d)

These compounds were prepared in the same way as described for 16a and 16b, starting from exo-5(R)-chloro lactone 13b (260 mg, 1.31 mmol) and racemic hydroxymethylenolactone 1519 (200 mg, 1.31 mmol). Yield 155 mg, 38% of slow moving diastereomer 16c as a white solid and 146 mg, 35% of fast moving diastereomer 16d as a white solid. Both compounds were recrystallized from hexane/ethyl acetate to obtain analytically pure samples.

16c Mp 211.5°C; [α]D +262° (c 0.18, CHCl3); Analysis calcd for C18H18O5: C, 68.78; H, 5.77. Found: C, 68.81; H, 5.80. 1H-NMR and mass data were the same as for compound 16b.

16d Mp 181.5-182°C; [α]D -173° (c 0.18, CHC13); Analysis calcd for C18H18O5: C, 68.78; H, 5.77. Found: C, 68.71; H, 5.60. 1H-NMR and mass data were the same as for compound 16a.

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(R)-ylxymethylene)-3,3α(R),6α(R)-tetrahydrocyclopenta[b]furan-2-one (4a)

Fast moving cycloadduct 16a (66 mg, 0.21 mmol) was dissolved in o-dichlorobenzene (25 mL) and heated at 180°C for 15 h. The solvent was removed in vacuo. The residue was purified by flash chromatography (SiO2, hexane / ethyl acetate 2:1) to give the diastereomer 4a (34 mg, 64%) as a white solid. All analytical data (Mp, [α]D, 1H-NMR, and mass data) were in complete agreement with those reported previously 19.

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(R)-ylxymethylene)-3,3α(S),6α(S)-tetrahydrocyclopenta[b]furan-2-one (4b)

Prepared starting from the slow moving cycloadduct 16b (30 mg, 0.095 mmol) in the same way as described for the synthesis of 4a. Yield 14 mg, 59% of 4b as a slightly yellow oil. All analytical data ([α]D, 1H-NMR, and mass data) were in complete agreement with those reported previously19.

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(S)-ylxymethylene)-3,3α(R),6α(R)-tetrahydrocyclopenta[b]furan-2-one (4c)

Prepared starting from the slow moving cycloadduct 16c (65 mg, 0.21 mmol) in the same way as described for the synthesis of 4a. Yield 34 mg, 66% of 4c as a slightly yellow oil. All analytical data ([α]D, 1H-NMR, and mass data) were in complete agreement with those reported previously19.

3-(4-Methyl-5-oxo-2,5-dihydro-furan-2(S)-ylxymethylene)-3,3α(S),6α(S)-tetrahydrocyclopenta[b]furan-2-one (4d)

Prepared starting from the fast moving cycloadduct 16d (60 mg, 0.19 mmol) in the same way as described for the synthesis of 4a. Yield 24 mg, 51% of 4d as a white solid. All analytical data (Mp, [α]D, 1H-NMR, and mass data) were in complete agreement with those reported previously19.

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