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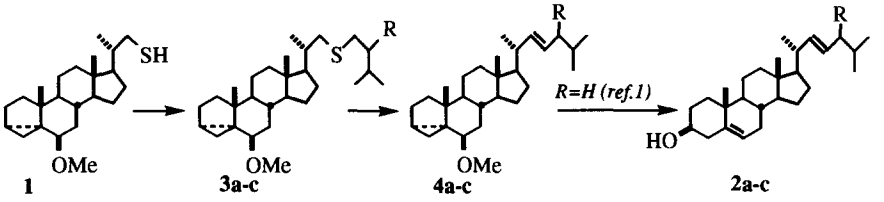
A Formal Synthesis of Brassinolide

T. Schmittberger and D. Uguen*

Laboratoire de Synthèse Organique, associé au CNRS
Ecole Européenne de Chimie, Polymères et Matériaux, Université Louis Pasteur
1, rue Blaise Pascal; 67008 Strasbourg (France)

Abstract: *Enzyme-catalysed differentiation of hydroxy groups in a C_{2V}-shaped tetraol-sulfide, combined with a* E*-stereoconvergent Ramberg-Bäcklund process, allowed to prepare pure (2S)-2,3-dimethyl-1-iodobutane, which could be coupled with a 3,5-cyclopregnane-20-thiomethanol derivative so as to give an efficient precursor of the title vegetal hormone.* © 1997 Published by Elsevier Science Ltd.

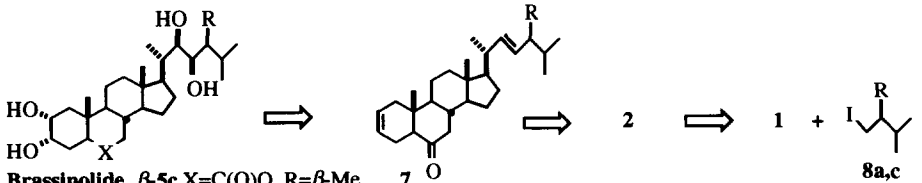
We have shown recently that the use of the Ramberg-Bäcklund rearrangement (RBR) allowed a convenient preparation of the side chain of sterols.[1] For instance, alkylation of thiol **1**, accessible in a few steps from stigmasterol -*i.e.* *β*-**2a**- by isoamyl iodide, gave the sulfide **3b** (R=H), which, by a short sequence involving a chlorination, an oxidation, and treatment of the resulting chlorosulfone with excess *t*-BuOK afforded selectively the unsaturated compound **4b**, efficiently converted into Δ^{22} dehydrocholesterol **2b**.



1 **3a-c** **4a-c** **2a-c**

a: R=Et; b: R=H; c: R=Me

As part of our ongoing work on the synthesis of modified steroids, we planned to develop that methodology to prepare brassinolide (*i.e.* *β*-**5c**). This lactone is a useful plant-growth factor and various approaches have been accordingly proposed to obtain this scarcely-distributed steroid from the more accessible stigmasterol, which indeed can be converted into the ketone *β*-**7c**, then into castasterone *β*-**6c**, an immediate precursor of *β*-**5c**.[2] The above RBR strategy seemed apt to rival existing hemisynthetic processes but, as it appears below, implementation of such a plan necessitated prior unfolding of an efficient access to the iodide (*S*)-**8c**.



Brassinolide, *β*-**5c** X=C(O)O, R=*β*-Me
Castasterone, *β*-**6c**, X=CO, R=*β*-Me

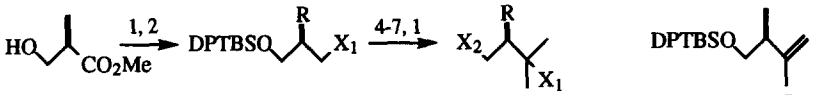
7

8a,c

(a-c as above)

We describe herein a method allowing to prepare conveniently the iodide **8c** as well as a related 2-substituted 1-iodo-3-methylbutane (*e.g.* (*R*)-**8a**), which paves the way for a general access to a wide range of branched steroids.

The iodide (*S*)-**8c** (R=Me) was first prepared by a classical chiron approach, starting from commercial methyl ester of (*R*)-hydroxyisobutyric acid (*R*)-**9c** which was converted to the alcohol (*S*)-**10c**, then to the iodide (*R*)-**11c** as described previously.[3] Treatment of (*R*)-**11c** by PhSNa furnished the sulfide (*R*)-**12c**, which was oxidised (MCPBA) to the sulfone (*R*)-**13c**. Bis-methylation of (*R*)-**13c** (BuLi/ICH_3) gave the sulfone (*R*)-**14c**, which, by hydrogenolysis of the phenylsulfonyl group (Mg/ethanol), followed by desilylation afforded the alcohol (*S*)-**16c**. Treating (*S*)-**16c** by PPh_3/I_2 delivered the target iodide (*S*)-**8c**.



(*R*)-**9c**

(R, a and c as defined precedently)

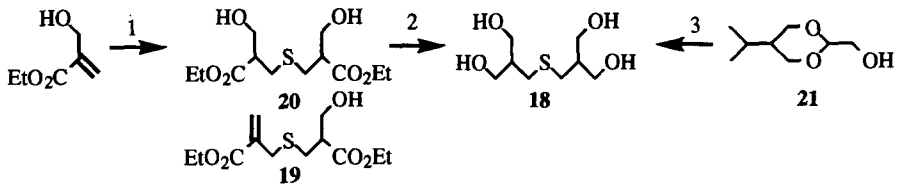
(*S*)-**10**, X_1=OH
(*R*)-**11**, X_1=I
(*R*)-**12**, X_1=SPh
(*R*)-**13**, X_1=SO_2Ph

(*S*)-**8**, X_1=H; X_2=I
(*R*)-**14**, X_1=SO_2Ph; X_2=ODPTBS
(*S*)-**15**, X_1=H; X_2=ODPTBS
(*S*)-**16**, X_1=H; X_2=OH

17

Reagents and conditions: 1- DPTBSCl (1.05 eq.), imidazole (3 eq.), DMF; r.t., 12 hours; 2- DIBA-H (2.1 eq.), CH_2Cl_2; -78°C, 2 hours; 3- PPh_3 (1 eq.), I_2 (1 eq.), imidazole (1 eq.); 4/1 ether/acetonitrile; r.t., 1 hour; 4- PhSNa (1.3 eq.), EtOH; r.t., 2 hours; 5- BuLi (1 eq.), ICH_3 (1 eq.), THF; -78°C, 0.5 hour, then same treatment (reagents added in situ), -78°C to r.t., 1 hour; 6- TBAF (1.5 eq.), THF; r.t., 5 hours; 7- Mg (5 eq.), $HgCl_2$ (cat.), EtOH; r.t. overnight.

A more enticing breakthrough resulted from the enzyme-catalysed acetylation of the C_{2v}-shaped tetraol **18**, which was prepared, as indicated, by alumina-catalysed addition of H_2S to the ethyl ester of 2-hydroxymethylacrylic acid and, after separation by column chromatography of the unsaturated sulfide **19**, which formed invariably as a side-product in that addition step, by subsequent LAH reduction of the resulting diester **20**. For larger scale preparation, an alternative, somewhat longer, procedure involving sequential treatment of the acetal **21**[5] by PPh_3/I_2 and Na_2S, followed by hydrolysis was preferred.



20

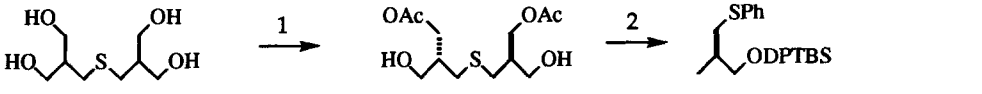
19

18

21

Reagents and conditions: 1- H_2S, basic alumina, CH_2Cl_2; r.t., 12 hours (37%); 2- LAH (4 eq.), THF; r.t., 4 hours (55%); 3- *i*) PPh_3 (1 eq.), I_2 (1 eq.), imidazole (1 eq.); 4/1 ether/acetonitrile; 0°C-r.t., 0.5 hour (87%); *ii*) Na_2S-$9H_2O$ (0.5 eq.), EtOH; r.t., 2 days (80%); *iii*) 1N HCl; 110°C, with continuous distillation of volatiles (95%).

Tetraol **18** was stirred with vinyl acetate and *Pseudomonas fluorescens* lipase in THF. The acetylation process was relatively fast, compared to what had been observed previously with related polyols.[6] After 6 days, at what time tetraol **18** had almost (not entirely) disappeared, the acetylation process was disrupted by filtration on Celite. Evaporation of solvents, followed by column chromatography resulted in the isolation of a diacetate, which proved to be (*R,R*)-**22**, with $[\alpha]_D$ +21 in a fairly good yield (78%). Noteworthy, any corresponding *meso* diacetate failed to be detected (^{13}C NMR) in the crude product, which was indicative of a deserving stereoselectivity.[6]



18

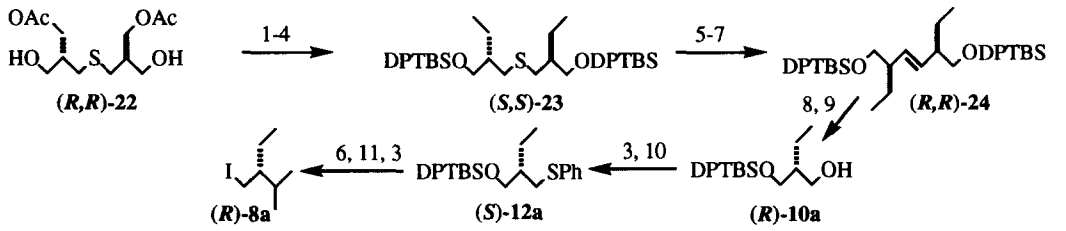
(*R,R*)-**22**, [α] D +21 (c=4 CH_2Cl_2)

(*R*)-**12c**, [α] D -11 (c=6 CH_2Cl_2)

Reagents and conditions: 1- PFL, vinyl acetate, THF; 5-10°C, 6 days (78%); 2- *i*) DPTBSCl (1.05 eq.), imidazole (3 eq.), DMF; r.t., 8 hours (93%); *ii*) Ni-R, EtOH; 50°C, 12 hours (93%); *iii*) K_2CO_3 (2 eq.), MeOH; -10°C, 2 days (88%); *iv*) PPh_3 (1 eq.), I_2 (1 eq.), imidazole (1 eq.); 4/1 ether/acetonitrile; r.t., 2 hours (89%); *v*) PhSNa (1.3 eq.), EtOH; r.t., 2 hours (92%).

Both the nature and the level of the enantioselectivity of that acetylation process were ascertained as follows. Protection of free hydroxy groups of compound (*R,R*)-**22** as DPTBS ether, then desulfuration (Raney-nickel), and hydrolysis of the acetate functionalities in mild conditions (MeOH/K_2CO_3) afforded the alcohol (*S*)-**10**, which by treatment with PPh_3/I_2, then with PhSNa gave the pure sulfide (*R*)-**12c**, identical ($[\alpha]_D$, NMR) to that obtained previously starting from *R*-**9c** and which could eventually be converted to the iodide (*S*)-**8c** as above.[7] Though lengthier to some extent than the preceding approach, that double-meso strategy proved to be of interest however for preparing a large amount of iodide (*S*)-**8c** since the use of the rather expensive ester (*R*)-**9** was avoided.

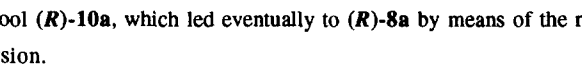
A more distinctive advantage, which is made clear in the next scheme, lies in the possibility of preparing likewise -i.e. *from the same diacetate* (*R,R*)-**22**- the iodide (*R*)-**8a**.



1- DPTBSCl (1.05 eq.), imidazole (3 eq.), DMF; r.t., 12 hours (92%); 2- K_2CO_3 (2 eq.), MeOH; -10°C, 2 days (88%); 3- PPh_3 (1 eq.), I_2 (1 eq.), imidazole (1 eq.); 4/1 ether/acetonitrile; r.t., 1 hour (91%); 4- MeMgBr (2.4 eq.), Li_2CuCl_4 (0.17 eq.), THF; -78°C- r.t., 18 hours (86%); 5- NCS (1 eq.), CCl_4; 90°C, 15 mn; 6- MCPBA (3 eq.), $NaHCO_3$ (6 eq.), CH_2Cl_2; r.t., 3 hours; 7- *t*-BuOK (4 eq.), THF; -78°C to 0°C, 3 hours (81%); 8- O_3, pyridine (0.5 eq.), DMS (1.47 eq.), CH_2Cl_2; -78°C; 9- DIBAH (2 eq.), CH_2Cl_2; -78°C, 2 hours (78%); 10- PhSNa (1.3 eq.), EtOH; r.t., 2 hours (92%); 11- *i*) BuLi (1 eq.), ICH_3 (1 eq.), THF; -78°C, 0.5 hour, then same treatment (reagents added in situ), -78°C to r.t., 1 hour (89%); *ii*) TBAF (1.5 eq.), THF; r.t., 5 hours (100%); *iii*) Mg (5 eq.), $HgCl_2$ (cat.), EtOH; r.t. overnight (78%).

Performing consecutively on (*R,R*)-**22a** a DPTBS protection, a saponification (K_2CO_3/MeOH), an iodination (PPh_3/I_2), and a methylation (MeMgBr/Li_2CuCl_4) afforded the bis-protected derivative (*S,S*)-**23** which led to the unsaturated compound (*R,R*)-**24** when submitted to RBR conditions. Ozonolysis of (*R,R*)-**24**, followed by DIBAH reduction provided the alcool (*R*)-**10a**, which led eventually to (*R*)-**8a** by means of the reaction sequence used for the (*R*)-**12c**-(*S*)-**8c** conversion.

Finally, the planned synthesis of β-**4c** was completed by alkylating the thiol **1** by iodide (*S*)-**8c** and submitting the resulting sulfide β-**3c** to *E*-selective RBR conditions, which afforded the pure (^{13}C NMR) crinostene derivative β-**4c** in a satisfactory 83% yield.



(*S*)-**8c**

Reagents and conditions: 1- NaH (1 eq.), DMF; r.t., 1 hour; 2- reagents 5-7 of the preceding scheme.

In conclusion, the combined use of a highly-enantioselective enzyme-catalysed acetylation of a double-meso-shaped tetrakis-hydroxymethyl sulfide and of *E*-selective RBR conditions permitted an efficient conversion of stigmasterol into the more elaborate branched-chain steroid β-**4c**, an effective precursor of brassinolide.

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References and Notes

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2- Lakhvich, F. A.; Kripach, V. A.; Zhabinskii, V. N. *Russian Chem. Rev.* **1991**, *60*, 658-675, and references therein.

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4- Lee, G. H.; Choi, E. B.; Lee, E.; Pak, C. S *Tetrahedron Lett.* **1993**, *34*, 4541-4542. The use of NaHg/MeOH induced the formation of compound **17** as a side-product.

5- m.p. 53-55°C; obtained by LAH reduction of the methyl ester of the corresponding carboxylic acid (prepared according to Eliel, E. L.; Banks, H. D. *J. Am. Chem. Soc.* **1972**, *94*, 171-176).

6- Breuilles, P.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4205-4208.

7- *Selected data*: **(*S*)-10c**: $[\alpha]_D$ -4 (c=8); C, H (%): 73.09, 8.69 (calc.: 73.12, 8.59); ^1H NMR: 0.83 (d, J=6.9Hz, 3H), 1.07 (s, 9H), 1.96-2.06 (m, 1H); 2.61, s, 1H), 3.56-3.78 (m, 4H); 7.36-7.46 (m, 6H), 7.64-7.75 (m, 4H); ^{13}C NMR (13.4, 19.3, 27, 37.6, 67.5, 68.6, 127.9, 129.9, 133.3, 135.7; **(*R*)-12c**: $[\alpha]_D$ -11 (c=7); ^1H NMR: 107 (d, 3H, J=6.7Hz), 1.12 (s, 9H), 1.97-2.07 (m, 1H), 2.72-2.82 (dd, J=7.6, 13Hz), 3.28-3.38 (dd, J=5.5, 13Hz, 1H), 3.57-3.65 (dd, J=5.7, 10Hz), 3.69-3.76 (dd, J=5, 10Hz), 7.14-7.51 (m, 11H), 7.69-7.74 (m, 4H) (adding $Eu(hfc)_3$ to the NMR tube failed to reveal the presence of the corresponding enantiomer); ^{13}C NMR: 16.5, 19.5, 27, 35.9, 37.2, 67.6, 125.6, 127.8, 128.9, 129.8, 133.8, 135.7, 137.4; **(*R*)-13c**: $[\alpha]_D$ -16 (c=5); C, H (%): 68.99, 7.2 (calc.: 68.98, 7.12); ^1H NMR: 1.02 (s, 9H), 1.08 (d, J=6.8Hz, 3H); 2.22-2.26 (m, 1H), 2.85-2.96 (dd, J=8.5, 14.2Hz, 1H), 3.38-3.51 (m, 2H), 3.56-3.63 (dd, J=4.4, 10.2Hz, 1H), 7.14-7.51 (m, 13H), 7.69-7.74 (m, 2H); 16.7, 19.3, 26.9, 27, 31.8, 59.2, 67.4, 127.8, 128, 129.4, 129.9, 133.3, 133.6, 135.6, 140.1; **(*R*)-14c**: ^1H NMR: 1.09 (s, 9H); 1.28 (d, J=7Hz, 3H), 1.31 (s, 3H), 1.37 (s, 3H), 2.22-2.26 (m, 1H), 3.68-3.76 (dd, J=6.1, 10.2Hz, 1H), 3.87-3.94 (dd, J=3.6, 10.2Hz, 1H), 7.35-7.7 (m, 13H), 7.83-7.87 (m, 2H); ^{13}C NMR: 14, 19.4, 20.1, 20.4, 27, 38.8, 65.9, 66.1, 127.8, 128.8, 129.8, 130.5, 133.4, 133.5, 135.8, 136.4; **(*S*)-15c**: $[\alpha]_D$ +3 (c=3); C, H (%): 77.6, 9.38 (calc.: 77.58, 9.47); ^1H NMR: 0.85 (d, 3H), 0.93 (d, J=6.8Hz, 6H), 1.13 (s, 9H), 1.55-1.71 (m, 1H), 1.76-1.89 (m, 1H), 3.51-3.59 (dd, J=6.5, 9.9Hz, 1H); 3.62-3.7 (dd, J= 6.1, 9.9Hz, 1H), 7.38-7.52 (m, 6H), 7.7-7.78 (m, 4H); ^{13}C NMR: 12.9, 18.3, 19.5, 20.9, 27.1, 28.9, 41.6, 67.5, 127.7, 129.6, 134.3, 135.8; **(*S*)-16c**: $[\alpha]_D$+5 (c=3); ^1H NMR: 0.81 (d, J=6.8Hz, 3H), 0.83 (d, J=6.9Hz, 3H), 0.88 (d, J=6.8Hz, 3H), 1.41-1.53 (m, 1H), 1.6-1.73 (m, 1H), 1.82 (s, 1H (OH)), 3.36-3.44 (dd, J=6.9, 10.5Hz, 1H), 3.52-3.6 (dd, J=5.9, 10.5Hz, 1H); ^{13}C NMR: 12.6, 18, 20.7, 28.7, 41.4, 66.6; **(*S*)-8c**: $[\alpha]_D$ +2 (c=7); ^1H NMR: 0.86 (d, J=6.7Hz, 3H), 0.9 (d, J=6.8Hz, 3H), 0.96 (d, J=6.6Hz, 3H), 1.31-1.41 (m, 1H), 1.59-1.72 (m, 1H), 3.11-3.2 (dd, J=6.9, 9.6Hz, 1H), 3.23-3.3 (dd, J=5, 9.6Hz, 1H); ^{13}C NMR: 14.1, 16.1, 18.1, 20.5, 32.1, 41.1; **18**: m.p. 51.5-53°C; C, H (%): 44.64, 8.53 (calc.: 45.69, 8.62); ^1H NMR (CD_3OD): 1.76-1.89 (m, 2H), 2.58 (d, J=6.8Hz, 4H), 3.63 (d, J=5.6Hz, 8H), 4.87 (m, 4H (OH)); ^{13}C NMR: 32.2, 45, 62.9; **(*R,R*)-22**: $[\alpha]_D$ +12 (c=5); C, H (%): 53.01, 8.16 (calc.: 53.22, 8.12); ^1H NMR: 1.35 (t, J=7Hz, 3H), 1.88- 2.03 (m, 2H), 2.07 (s, 6H), 3.57-3.62 (m, 4H), 4.02-4.17 (m, 4H); ^{13}C NMR: 20.9, 26.1, 37.7, 62.3, 64.8, 171.4; **(*S,S*)-23**: $[\alpha]_D$ -2 (c=6); C, H (%): 73.7, 8.64 (calc.: 73.84, 8.56); ^1H NMR: 0.87 (t, J=7.2Hz, 6H), 1.08 (s, 18H), 1.43-1.61 (m, 4H), 1.63-1.69 (m, 2H), 2.55 (dd, J=6, 9.6Hz, 2H), 3.65 (dd, J=5.2, 10Hz, 2H), 3.73 (dd, J=4.6, 10Hz, 2H), 7.34-7.47 (m, 12H), 7.65-7.73 (m, 8H); ^{13}C NMR: 11.5, 19.4, 23.3, 27, 34.8, 42.4, 64.8, 127.7, 129.7, 133.9, 135.8; **(*R,R*)-24**: C, H (%): 77.82, 8.61 (calc.: 77.72, 8.69); ^1H NMR: 0.87 (t, J=7.5Hz, 6H), 1.05 (s, 18H), 1.23-1.37 (m, 4H), 1.61-1.74 (m, 2H), 3.49-3.77 (m, 4H), 5.24-5.3 (m, 2H); 7.3-7.45 (m, 12H), 7.65-7.72 (m, 8H); **(*R*)-10a**: $[\alpha]_D$ +15 (c=2); C, H (%): 73.49, 8.84 (calc.: 73.63, 8.82); ^1H NMR: 0.86 (t, J=6.4Hz, 3H), 1.08 (s, 9H), 1.19-1.33 (m, 2H), 1.65-1.76 (m, 1H), 2.68 (s, 1H (OH)), 3.62-3.86 (m, 4H), 7.37-7.5 (m, 6H), 7.68-7.72 (m, 4H); ^{13}C NMR: 11.8, 19.3, 20.7, 27, 44.1, 65.9, 67.1, 127.7, 129.9, 133.2, 135.7; **(*S*)-12a**: ^1H NMR: 0.85 (t, J=7.3Hz, 3H), 1.07 (s, 9H), 1.47-1.58 (m, 2H), 1.7-1.77 (m, 1H), 2.93 (dd, J=6.4, 12.8Hz, 1H), 3.63 (dd, J=5.8, 10.1Hz, 1H), 3.78 (dd, J=4.3, 10.1Hz, 1H), 7.15-7.49 (m, 11H), 7.66-7.71 (m, 4H); ^{13}C NMR: 11.4, 19.4, 24, 27, 35.2, 42.2, 64.6, 125.5, 127.7, 128.7, 128.8, 129.7, 133.7, 135.7, 137.5; **(*R*)- 16a**: $[\alpha]_D$ +9 (c=2); ^{13}C NMR: 12.2, 19.3, 19.8, 20.3, 27.6, 48.3, 63.1; **β-3c**: $[\alpha]_D$ +80 (c=5); C, H (%): 77.99, 11.16 (calc.: 77.96, 11.28); ^{13}C NMR: 12.4, 13.2, 15.3, 18, 18.4, 18.9, 20.4, 21.5, 22.6, 24.3, 25, 28.3, 30.6, 31.5, 33.4, 35.1, 35.3, 36.8, 38.3, 39, 40.2, 43.1, 43.4, 48.1, 55.7, 56.4, 56.6, 82.4; **β-4c**: $[\alpha]_D$ +42 (c=4); C, H (%): 84.3, 11.78 (calc.: 84.4, 11.72); ^{13}C NMR: 12.5, 13.2, 18.2, 19.4, 19.7, 20.3, 21.1, 21.6, 22.9, 24.3, 25.1, 29, 30.6, 33.3, 33.5, 35.2, 35.4, 40.3, 40.4, 42.8, 43.2, 43.5, 48.2, 56.2, 56.7, 57.7, 131.9, 136.2. Excepted as otherwise stated, ^1H and ^{13}C NMR spectra were recorded at 200 and 50MHz, respectively, on $CDCl_3$ solutions. All $[\alpha]_D$ refer to CH_2Cl_2 solutions and were measured at 21°C

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