Pergamon

Tetrahedron Letters 43 (2002) 3169–3173

TETRAHEDRON LETTERS

Toward a total synthesis of brassinosteroids; structure assessment of the Ireland–Claisen products of geranyl and neryl esters

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Received 13 February 2002; accepted 7 March 2002

Abstract—As estimated by ^{1}H NMR analysis, thermal isomerisation of the kinetic silylenolate derived from the ester (*Z*)-**8a** proceeds with acceptable diastereo and facial selectivity, thence affording an acid having the required absolute configuration for further elaboration to brassinosteroids.

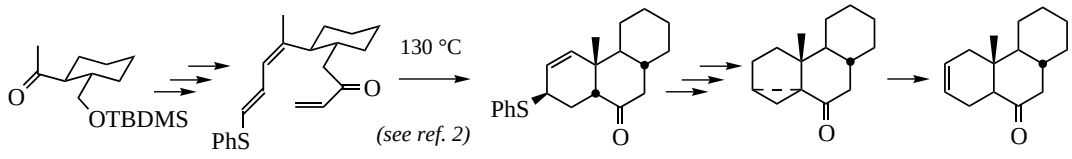
Due to its activity as a plant-growth promoter and, accordingly, to its potential use in agriculture, brassinolide **1a** has given rise over the past 20 years to a substantial research activity towards a better understanding of its biological activity and the development of efficient ways to obtain this scarce material from more available steroids.[1] To date, however, no total synthesis of either **1a** or its biosynthetic precursor castasterone **1b** has appeared.

As part of our continuing effort to synthesise brassinosteroids,[2] we have shown previously how a hydrophenanthrone featuring the A–B–C ring system of the ketone **2** could be prepared by means of intramolecular Diels–Alder reaction of a dienylsulfide (Scheme 1).[2a]

This result, coupled with those previously obtained in the elaboration of compound **3** to the ketone **2** and thus to brassinosteroids,[1,2b] led us accordingly to examine the preparation of the nitrile **5**, whose transformation into the sulfide **4**, a potential precursor of the ketone **2**, thus appeared feasible (Scheme 2).

In light of recent, related, results,[3] free radical cyclisation of the iodide **6a** could reasonably be considered as a possible way to obtain **5**. In the event, the only challenging aspect of this plan appeared to be the preparation of this iodide and thus of the acid (*R*,*S*)-**7a**, from which it could derived by two one-carbon homologations. This letter describes how this acid may be obtained by Ireland–Claisen (IC) rearrangement of the ester (*Z*)-**8a**, the conditions permitting elaboration of this acid to the target hydrindane derivative **5** being described in the accompanying letters.

As can be seen in Scheme 3, assuming that the planned rearrangement would proceed according to the currently-accepted model[4] and, moreover, that the R_1R_2CH group of the *Z* and the *E* silylenolate (L = ligand; R_1 = Me, R_2 = CH_2OTIPS) derived from *E*-**8a** and *Z*-**8a**, respectively, would adopt the indicated confor-



Scheme 1.

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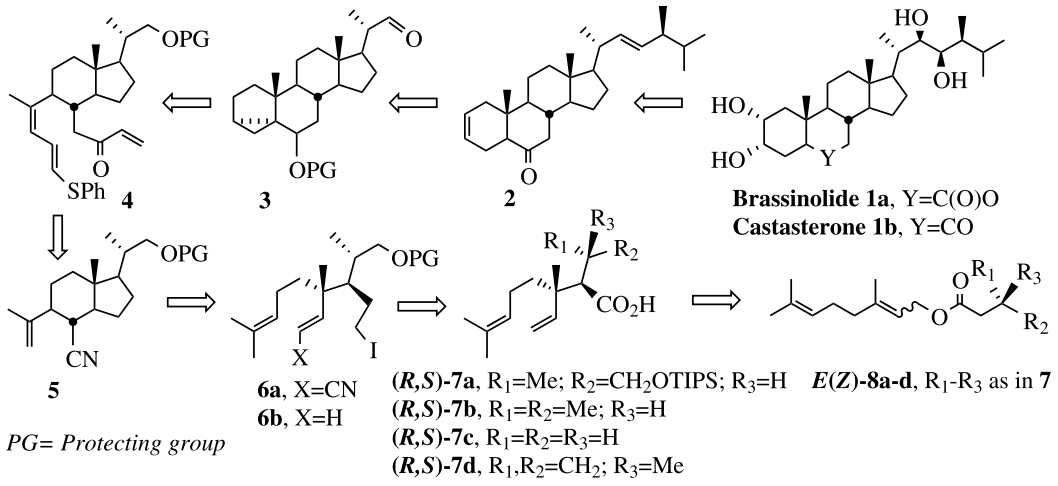
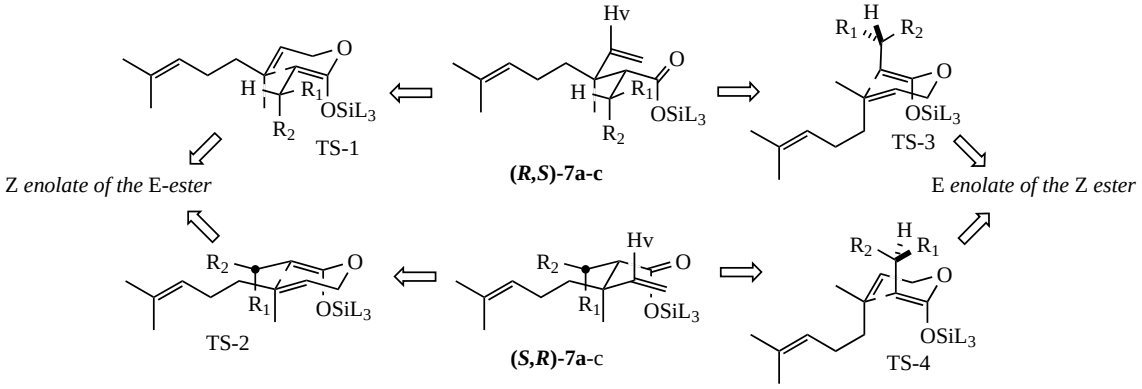


Scheme 2.



Scheme 3.

mation in each of the resulting four transition states (TS), it could be anticipated that those achieved by the *E* enolate of the *Z* ester (i.e. TS-3 and TS-4) would be lower in energy as compared with those resulting from the *Z* enolate of the *E* ester (i.e. TS-1 and TS-2) due to the development of an unfavourable pseudo 1,3-diaxial steric interaction in the latter two. Accordingly, generation of the kinetic (i.e. *E*) enolate derivative of *Z*-**8a** would be required in order to generate the *R*,*S* (or the *S*,*R*) configuration at the newly-formed stereogenic centres.

More difficult to predict was the face selectivity with which this IC rearrangement would proceed since the TS-3 intermediate, leading to the desired (i.e. (*R*,*S*)-**7a**) isomer appeared close in energy to TS-4.[5]

In order to assess the validity of this analysis and to design the analytical tool for assessing the stereoselectivity of these processes, we decided first to study the fate of the silylenolates generated from the simpler esters **8b** and **8c**. Examination of the literature revealed that the diastereomeric acids (*R*,*S*/*S*,*R*)-**7d** and (*R*,*R*/*S*,*S*)-**7d**, formed by IC rearrangement of the related *i*-pentenoic acid esters **8d**, could be clearly distinguished in ^{1}H NMR analysis;[6] the signal displayed by the vinylic hydrogen atom, designated by Hv in Scheme 3, resonates at higher field for the *R*,*R* (res. *S*,*S*) isomer than for the *R*,*S* (res. *S*,*R*) one in this series. It was therefore of interest to verify that this dichotomy in chemical shift was not related to the nature of the acyl component of the starting ester since integration of the relevant signals in the ^{1}H NMR spectrum would have allowed straightforward assessment of the diastereoselectivity of the rearrangement.

To this end, both the geranyl and the neryl propionates *E*-**7c** and *Z*-**7c** were independently submitted to both the 'kinetic' or 'thermodynamic' enolisation/silylation sequence and, after a hydrolysis, the resulting acid fractions were analysed by NMR.[7] As can be seen (Table 1), the signal displayed in the ^{1}H NMR spectrum by Hv of the major isomer formed from either *E*-**8c** or *Z*-**8c** under thermal and kinetic conditions, respectively (entries 2 and 3) appears at lower field compared with the minor product. On the basis of previous observations with the corresponding *i*-pentenoate (vide supra), and in keeping with our model (Scheme 3; R_1, $R_2 = H$), we assigned the *S*,*R* (res. *R*,*S*) configuration to this product.

The validity of this assumption was demonstrated as follows. The IC product obtained from *E*-**8c** under

Table 1. Selectivity of the IC rearrangement of esters **8b–c**

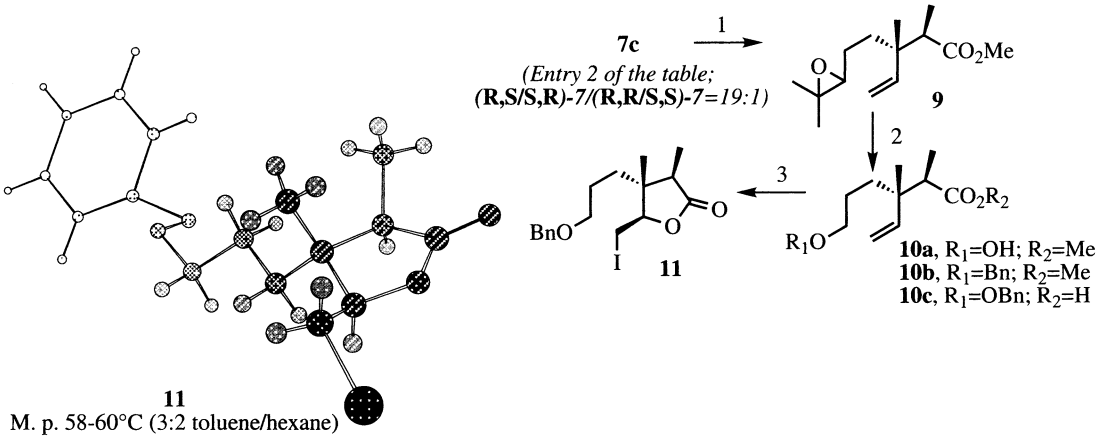
Entry	Substrate	Conditions[7] (assumed enolate)	Product, Rdt (%)	δHv (ppm) (major isomer)	(*R*,*S*/*S*,*R*)-**7**/(*R*,*R*/*S*,*S*)-**7**
1	*E*-**8c**	Kinetic (*E*)	**7c**, 57	5.68	1:4
2	*E*-**8c**	Thermodynamic (*Z*)	**7c**, 33	5.89	19:1
3	*Z*-**8c**	Kinetic (*E*)	**7c**, 57	5.89	4:1
4	*Z*-**8c**	Thermodynamic (*Z*)	**7c**, 48	5.68	1:5
5	*E*-**8b**	Kinetic (*E*)	**7b**, 77	5.77	1:4
6	*E*-**8b**	Thermodynamic (*Z*)	**7b**, 55	6.07	3:2
7	*Z*-**8b**	Kinetic (*E*)	**7b**, 90	6.07	46:1

thermodynamic conditions (entry 2) was esterified using CH_2N_2 (Scheme 4). Chromatography of the resulting ester mixture, followed by treatment with MCPBA of the major methyl ester thus obtained gave **9** as a mixture of two diastereomers, which was sequentially reacted with periodic acid and $NaBH_4$ to give **10a**. Conversion of **10a** into its *O*-benzyl derivative **10b** followed by treatment with *n*-PrSLi in HMPT furnished the acid **10c**, which afforded a crystalline iodolactone to which the structure **11** could unambiguously be assigned by X-ray analysis.[8]

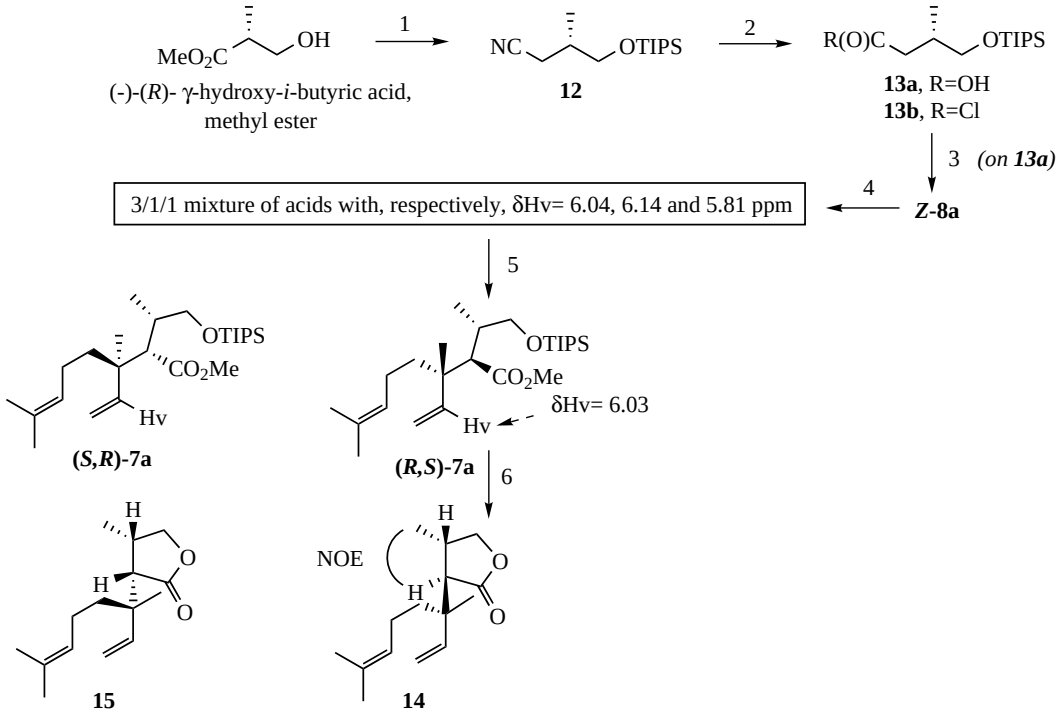
The *i*-valerates **8b** were then submitted to the same IC conditions, the resulting acid mixture in each case being analysed by NMR (entries 5–7 of Table 1). In perfect accord with the preceding results, the main component formed from either *E*-**8b** or *Z*-**8b** under thermodynamic and kinetic conditions displayed in the ^{1}H NMR spectrum a signal at lower field (δHv = 6.07 ppm), as compared with the value (δHv = 5.77 ppm) obtained for the minor compound. As also anticipated from the model (Scheme 3; $R_1 = R_2 = Me$), higher selectivity was observed with the neryl ester under kinetic conditions (entry 7). It can be concluded that whatever the level of ramification (**8c** versus **8b**), or unsaturation (**8b** versus **8d**), of the acyl component of the geraneryl (res. neryl) ester used, ^{1}H NMR can be used to determine the stereoselectivity of these IC rearrangements, with a signal at lower field for the Hv proton being indicative of the *R*,*S* (res. *S*,*R*) configuration.

Assuming that this would also apply to the IC product formed from the ester *Z*-**8a**, its preparation was achieved starting from the commercially-available methyl ester of (*R*)-γ-hydroxy-*i*-butyric acid (Scheme 5). Sequential treatment of this ester with tris-*i*-propylsilyl triflate (TIPSTf), DIBA-H, tosyl chloride and NaCN under standard conditions furnished the nitrile **12**. Reduction of **12** using DIBA-H, and oxidation of the aldehyde thus formed with sodium chlorite delivered the pure acid **13a**. Stirring **13a** with thionyl chloride then furnished the chloride **13b**, which was condensed with nerol in the presence of DMAP to afford *Z*-**8a**.

IC rearrangement of this compound under 'kinetic' conditions resulted in the isolation of an acid fraction whose NMR analysis indicated it was a 3/1/1 mixture of isomers with, respectively, δHv = 6.04, 6.14 and 5.81 ppm in the ^{1}H NMR spectrum. Esterification of this product with diazomethane and chromatography on silica gel of the resulting ester mixture (same isomeric ratio, as established both by ^{1}H NMR and GLC) afforded a fraction enriched in the methyl ester of the major acid, still containing, however, a small amount (<10%) of that formed from the minor product (δHv = 5.81).



Scheme 4. *Reagents and conditions*: 1. (i) CH_2N_2, ether; 0°C; (ii) chromatography on silica gel (hexane) (66%); (iii) MCPBA (1 equiv.), CH_2Cl_2; 0 to rt, 1 h (99%); 2. (i) H_5IO_6 (1 equiv.), THF; rt, 1 h; (ii) $NaBH_4$ (3.6 equiv.), EtOH; 0°C to rt, 30 min (86%); (iii) $BnOC(NH)CCl_3$ (1 equiv.), camphorsulfonic acid (1 equiv.), CH_2Cl_2; rt, 2 h, then, in five portions, each 3 h, $BnOC(NH)CCl_3$ (1 equiv.) (65%; from **9**); 3. (i) *n*-PrSLi (1 equiv.), HMPA (2 ml/mmol); rt, 5 h (80%); (ii) 0.5 M aqueous $NaHCO_3$ (6 ml/mmol), I_2 (1.5 equiv.) in 5 M aqueous KI; rt, 1 day, then partition in 0.25 M $Na_2S_2O_3$/ether (97%).



Scheme 5. *Reagents and conditions*: 1. (i) TIPSTf (1 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2; 0°C to rt, 5 h; (ii) DIBAH (2.2 equiv.), CH_2Cl_2; −78°C, 16 h; (iii) tosyl chloride (1.2 equiv.), pyridine (6 equiv.); 0–3°C overnight; (iv) NaCN (1.8 equiv.), DMSO; 80°C, 20 h; 2. (i) DIBA-H (1.2 equiv.), CH_2Cl_2; −78°C, 2 h; (ii) 30% H_2O_2 (1.1 equiv.), 4/1 acetonitrile/1 M KH_2PO_4 (aqueous), $NaClO_2$ (1.4 equiv.); 0°C, 15 min; 3. $SOCl_2$ (2 equiv.) DMF (two drops), ether; 0°C, 1 h, then evaporation, then nerol (1 equiv.), DMAP (1 equiv.), ether; 0°C, 30 min (83%); 4. see Ref. 7; 5. CH_2N_2 (excess), ether; 0°C, 0.5 h, then chromatography (hexane/ether) (31%, from *Z*-**8a**); 6. 1 M (in THF) TBAF (2 equiv.); rt, 3 h, then chromatography (9:1 hexane/ether) (96%).

That the major acid, with δHv = 6.04, was indeed the desired isomer (i.e. (*R*,*S*)-**7a**), those with δHv = 6.14 and 5.81 being then, respectively, (*S*,*R*)-**7a** and (*R*,*R* (or *S*,*S*))-**7a**, was simply established as follows.

Treatment of the preceding purified ester with TBAF in THF afforded a 9/1 mixture of lactones displaying in relevant NMR experiment a significant, indicated, NOE correlation for the major constituent, which, as shown, dismissed the structure **15**. It thus follows that the main lactone could only be **14** and not **15**. Hence the major IC product formed from *Z*-**8a** in kinetic conditions was, as predicted, (*R*,*S*)-**7a**.[9]

In conclusion, besides a further confirmation of the value of the model used for predicting the fate of these IC rearrangements, the results presented in this letter illustrate that ^{1}H NMR analysis of the acids formed by rearrangement of the silylenolates derived from geranyl and neryl esters *E*-**8** and *Z*-**8** constitutes a particularly convenient means for assessment of their structure. Moreover, though not proceeding with a complete stereoselectivity, this preparation of the acid (*R*,*S*)-**7a** permitted us to obtain useful amounts of a crucial intermediate of our planned synthesis of brassinosteroids in a single step from readily accessible starting compounds.

Acknowledgements

Thanks are due to the 'Ministère de la Recherche et de l'Education' for a grant (to O.T.).

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5. Rough calculation using the Chem3D® energy-minimisation package indicated, however, that in this case (i.e. R_1 = Me and R_2 = CH_2OTIPS) TS3 was somewhat lower in energy than TS4.
6. Frater, G. *Helv. Chim. Acta* **1978**, *61*, 2709–2719. For an asymmetric version of this rearrangement, see: Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026–4028.

7. The geranyl and the neryl esters described in this letter were prepared quantitatively by dropwise addition at 0°C of the acid chloride to an ether solution of geraniol (res. nerol; Fluka®) and pyridine (**7b–c**), or DMAP (**7a**), and were freshly purified prior to use by either distillation (**7b–c**) or chromatography (**7a**). *Protocol for 'kinetic' IC conditions*: To the cooled (ca. −78°C) mixture resulting from addition of 1.6 M (in hexane) *n*-BuLi (1.1 equiv.) to a solution of *i*-propyl-cyclohexylamine (0.5 ml) in THF (5 ml) at 0°C was added TMSCl (2.6 ml; 8 equiv.) diluted with THF (5 ml), followed immediately by the ester (2.5 mmol) in the same solvent (5 ml). After stirring (ca. 2 min), excess triethylamine (5 ml) was added. The temperature was maintained at −78°C for 10 min, then allowed to rise gradually to ca. 20°C followed by refluxing for 5 h. After cooling, the reaction mixture was added dropwise to iced 10% HCl (50 ml), and extracted with ether (3×20 ml). The combined organic layers were extracted with 1N NaOH (3×20 ml). The aqueous phases thus generated were combined, acidified to pH 1 with 5N HCl, then back-extracted with CH_2Cl_2 to afford, after drying ($MgSO_4$) and evaporation, the rearranged acid as a pale yellow oil. *Protocol for the 'thermodynamic' conditions*: strictly identical to that described by Ireland in Ref. 4.
8. Crystal data for **11** (mp 58–60°C): $C_{17}H_{23}IO_3$, mol. weight = 402.28, triclinic, space group *P*-1, $a = 7.267(2)$, $b = 10.183(3)$, $c = 12.322(3)$ Å, $\alpha = 79.54(2)$, $\beta = 78.82(2)$, $\gamma = 87.40(2)°$, $V = 882.5(4)$ Å^3, $Z = 2$, $D_{calcd} = 1.51$ g cm^{-3}, μ(Mo Kα) = 1.82 mm^{-1}. Data were collected using a Nonius Mach3 diffractometer, graphite monochromated MoKα radiation ($\lambda = 0.7173$ Å) at room temperature. 3781 reflections were collected using a crystal of 0.40×0.40×0.38 mm^3. Absorption corrections based on ψ-scans were applied. The structure was solved using direct methods and refined with 2022 reflections having $I > 3\sigma(I)$. Atom C7 is disordered over two positions in the ratio 1/1. Hydrogen atoms were introduced as fixed contributors at their computed coordinates (d(C–H) = 0.95 Å, B(H) = 1.3) with the exception of the C7 protons, omitted. Full matrix refinements against $|F|$. Final results: $R(F) = 0.039$ Å, $Rw(F) = 0.060$, GOF = 1.24, largest peak in final difference = 0.83 e Å^{-3}. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre for compound **11**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CN2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).
9. Selected data: (*R*,*S*/*S*,*R*)-**7c**: ^{1}H NMR: 1.07 (s, 3H), 1.11 (d, $J = 7$ Hz, 3H), 1.32–1.52 (m, 2H), 1.58 (s, 3H), 1.67 (s, 3H), 1.75–2 (m, 2H), 2.45 (q, $J = 7$ Hz, 1H), 4.92–5.13 (m, 3H), 5.89 (dd, $J = 11$, 17.5 Hz, 1H; *Hv*); ^{13}C NMR: 12.4, 17.5, 18.9, 22.7, 25.6, 38.8, 41.6, 48.3, 113.6, 124.5, 131.3, 143.3, 181.9; (*R*,*R*/*S*,*S*)-**7c**: ^{1}H NMR: 1.09 (m, 6H), 1.35–1.5 (m, 2H), 1.58 (s, 3H), 1.67 (s, 3H), 1.84–1.98 (m, 2H), 2.48 (q, $J = 7$ Hz, 1H), 4.94–5.16 (m, 3H), 5.68 (dd, $J = 11$, 17.5 Hz, 1H; *Hv*); **11**: ^{1}H NMR: 0.84 (s, 3H), 1.1 (d, $J = 7$ Hz, 3H), 1.53–1.57 (m, 4H), 2.47 (q, $J = 7$ Hz, 1H), 3.13–3.36 (m, 2H), 3.45–3.5 (m, 2H), 4.37 (dd, $J = 3.5$, 9.5 Hz, 1H), 4.51 (s, 2H), 7.29–7.37 (m, 5H); (*R*,*S*–*S*,*R*)-**7b**: ^{1}H NMR: 0.95 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 7$ Hz, 3H), 1.14 (s, 3H), 1.32–1.54 (m, 2H), 1.57 (s, 3H), 1.66 (d, $J = 1$ Hz, 3H), 1.81–1.95 (m, 2H), 1.97–2.07 (m, 1H), 2.24 (d, $J = 4.4$ Hz, 1H), 4.97 (dd, $J = 1.4$, 17.5 Hz, 1H), 5.03–5.12 (m, 2H), 6.07 (dd, $J = 10.9$, 17.5 Hz, 1H; *Hv*); ^{13}C NMR: 17.6, 20.2, 20.8, 22.8, 24.3, 25.7, 27.5, 39.6, 42, 60.9, 113.2, 124.6, 131.3, 144.1, 180.5; (*R*,*R*-*S*,*S*)-**7b**: ^{1}H NMR: 0.95 (d, $J = 6.7$ Hz, 3H), 1.01 (d, $J = 7$ Hz, 3H), 1.19 (s, 3H), 1.34–1.46 (m, 2H), 1.66 (d, $J = 0.9$ Hz, 3H), 1.81–2.04 (m, 3H), 2.25 (d, $J = 4.4$ Hz, 1H), 4.95–5.13 (m, 1H), 5.77 (dd, $J = 10.9$, 17.5 Hz, 1H; *Hv*); *Z*-**8a**: ^{1}H NMR: 0.95 (d, $J = 7$ Hz, 3H), 1–1.1 (m, 21H), 1.6 (s, 3H), 1.68 (s, 3H), 1.76 (d, $J = 1$ Hz, 3H), 2.03–2.17 (m, 6H), 2.45–2.57 (m, 1H), 3.49 (dd, $J = 6$, 9.5 Hz, 1H), 3.63 (dd, $J = 5.3$, 9.5 Hz, 1H), 4.56 (d, $J = 7.2$ Hz, 2H), 5.08–5.13 (m, 1H), 5.35 (dt, $J = 1$, 7.2 Hz, 1H); ^{13}C NMR: 12, 16.8, 17.7, 18.1, 23.6, 25.7, 26.7, 32.3, 33.4, 38.3, 60.7, 67.7, 119.4, 123.7, 131.8, 142.4, 174.4; (*R*,*S*)-**7a**, methyl ester: ^{1}H NMR: 1.01–1.18 (m, 24H), 1.12 (s, H), 1.23–1.36 (m, 2H), 1.56 (s, 3H), 1.65 (s, 3H), 1.83–2.02 (m, 3H), 2.35 (d, $J = 5$ Hz, 1H), 3.2–3.35 (m, 1H), 3.6 (s, 3H), 3.8 (dd, $J = 3.5$, 9.7 Hz, 1H), 4.9–5.11 (m, 3H), 6.03 (dd, $J = 17.5$, 10.9 Hz, 1H); ^{13}C NMR: 12, 17, 18.1, 19, 20.1, 22.8, 25.7, 35.3, 39.6, 42.2, 50.8, 58.6, 66.6, 113.1, 124.6, 131.4, 144.1, 174.1; **14**: (400 MHz, in C_6D_6): 0.52 (d, $J = 7$ Hz, 3H), 0.92 (s, 3H), 1.23–1.42 (m, 4H), 1.6 (s, 3H), 1.68 (s, 3H), 1.7–1.83 (m, 2H), 1.92 (d, $J = 5$ Hz, 1H), 1.97–2.11 (m, 1H), 3.06 (dd, $J = 5.5$, 8.5 Hz, 1H), 3.66 (t, $J = 8.5$ Hz, 1H), 4.78–4.96 (m, 2H), 5.19–5.24 (m, 1H), 5.7 (dd, $J = 17.5$, 10.9 Hz, 1H). Excepted as otherwise stated, ^{1}H and ^{13}C NMR at 200 and 50 MHz in $CDCl_3$, respectively. The results presented in this letter are taken in part from the thesis dissertation of Olivier Temmem (Strasbourg, December 2000).