Pergamon

Tetrahedron Letters 43 (2002) 3181–3184

TETRAHEDRON LETTERS

Toward a total synthesis of brassinosteroids; stereoselective generation of the hydrindane ring system

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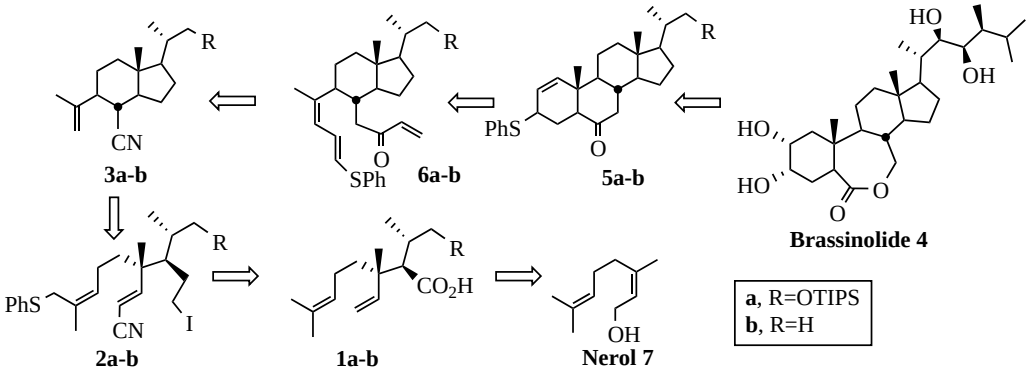
Received 13 February 2002; accepted 7 March 2002

Abstract—Cyclisation of the cyanoiodide **2b** under free-radical conditions affords the hydrindane derivative **3b** in good yield and with perfect selectivity, a result which paves the way for a total synthesis of brassinosteroids.

Having shown in a preceding letter[1a] how hindered olefins related to compound **1** could be converted into α,β-unsaturated nitriles by means of a chlorosulfanylation–cyanation sequence, we turned our attention to the preparation of the nitrile **2a** and, in the sequel, to its cyclisation to the hydrindane derivative **3a**, a crucial intermediate of our planned synthesis of brassinolide **4**. The methodology aimed at converting **3a** into **4** via **5a** and **6a** having previously been unveiled,[1b] execution of the **2**–**3** conversion would validate our plan (Scheme 1). We describe in this letter how these two steps were completed in the case of the closely-related acid **1b**, selected as a model substrate owing to the particular ease with which it can be prepared in large scale from nerol.[1b]

The installation of a cyano group as envisaged the **1b**–**2b** conversion of the above sequence could not been effected without first protecting the trisubstituted carbon–carbon double bond of **1b**, as this would be more reactive toward the electrophilic PhSCl reagent. Epoxidation of this unsaturation offered a very convenient solution since the oxiran ring thus generated could serve later to install the needed allyl sulfide functionality (vide infra). However, due to the sensitivity of epoxides to reducing reagents, conversion of the carboxylic group of **1b** into a haloethyl residue had to be executed first, which was achieved by standard conditions (Scheme 2).

Sequential treatment of **1b** by LAH, tosyl chloride and sodium cyanide afforded the cyanide **8a**, which, by two successive reductions, first with DIBAH, then with $NaBH_4$, gave the alcohol **8b**. Tosylation of **8b** and ensuing substitution with LiCl afforded the chloride **8c**, the overall process being performed on a 20 g scale



Scheme 1.

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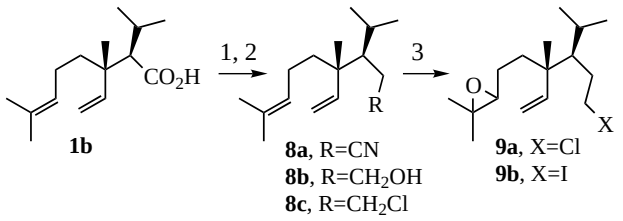


Scheme 2. *Reagents and conditions*: 1. (i) LAH (3 equiv.), THF; reflux, 20 h (99%); (ii) tosyl chloride (1 equiv.), pyridine (6 equiv.); 4°C, overnight (91%); (iii) NaCN (1.8 equiv.), DMSO; 80°C, 10 h (80%); 2. (i) DIBAH (1.2 equiv.), CH_2Cl_2; −78°C, 2 h (97%); (ii) $NaBH_4$ (1 equiv.), EtOH; rt, 2 h (89%); (iii) same conditions as in 1 (ii); (iv) LiCl (10 equiv.), DMSO; 80°C, 3 h (90%, from **8a**); 3. MCPBA (1.1 equiv., in 2 portions), CH_2Cl_2; 0°C, 30 min, then rt, 2 h (96%).

without difficulty. Finally, reacting **8c** with MCPBA afforded **9a** as a 1:1 mixture of diastereomers (NMR).

This epoxide was then reacted with PhSCl to form the chlorosulfide **10a** (Scheme 3). The sensitivity of related chlorosulfides to silica gel has already been noted[1a] and, indeed, stirring **10a** with silica gel in CH_2Cl_2 for two days slowly induced the appearance of the isomeric chlorosulfide **10d** (14%), as well as the tetrahydropyran **11** (10%). However, contrary to observations with neohexene, attempted column chromatography of the crude reaction mixture for the sake of characterisation afforded pure **10a** (87%), no trace of rearranged product being detected under these conditions.

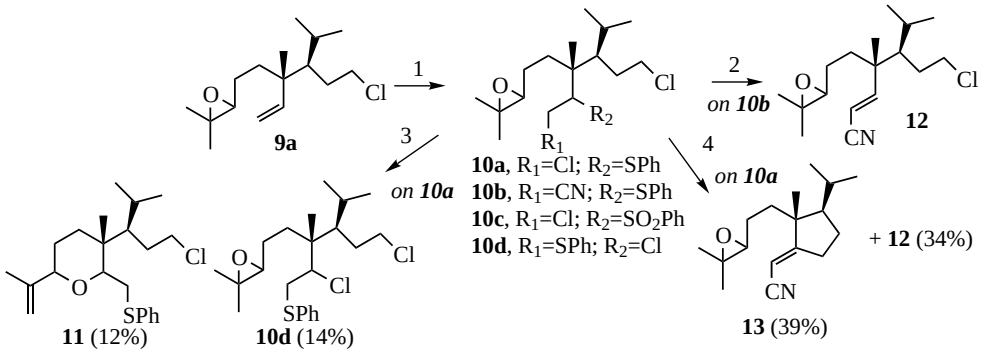
Not too surprisingly given the exceptional congestion of its chlorosulfide functionality, in situ treatment of crude **10a** by *N*-tetrabutylammonium cyanide (TBACN) induced extensive reversion of the sulfanylation process to give the desired cyanosulfide **10b** as a 1:1 mixture (NMR) with the starting chloride **9a**. However, by fractionating this mixture (column chromatography) and repeating twice the preceding chlorosulfanylation–cyanation sequence on recovered **9a**, the cyanosulfide **10b** was obtained in a satisfactory 91% combined yield. Treatment of **10b** with MCPBA under basic conditions (Na_2CO_3) then gave the desired unsaturated nitrile **12** (98%), a similar yield being achieved by first reacting the crude **9a**/**10b** mixture with the MCPBA·Na_2CO_3 reagent, purifying the formed **9a**/**12** mixture by chromatography and then re-submitting recovered **9a** to a sulfanylation–cyanation–oxidation sequence.

Attempts to shorten the above process by using the alternative oxidation–cyanation procedure[1a] proved unrewarding. At variance with results obtained with neohexene, treatment by KCN in DMSO of the chlorosulfone **10c**, prepared by treating **10a** with MCPBA (87%), produced only reduced amounts (34%) of unsaturated nitrile (i.e. **12**), the preferred pathway being the formation of the cyclopentane derivative **13** (39%).[2]

The allyl sulfide functionality was then installed by treating the nitrile **12** with aluminium isopropoxide in refluxing toluene, the allylic alcohol **14** which formed almost quantitatively (98%) being reacted sequentially with $SOCl_2$ in ether, PhSLi in DMF, and finally excess NaI in hot butanone to give, after purification by chromatography, the sulfide **2b** as a mixture of diastereomers ($E/Z = 9{:}1$; NMR).

The planned cyclisation was then attempted by reacting **2b** with excess hexabutylditin in refluxing benzene (**2b** = 0.01 M) and under irradiation (Sunlight lamp) to give a single product after three days (75%) to which the structure **3b** was tentatively assigned (NMR). This was unequivocally confirmed by sequentially treating this nitrile with DIBAH and $NaBH_4$. Thorough NMR analysis (COSY, TOCSY, HMQC) of the alcohol thus produced clearly indicated it had the structure **15a**.

A plausible explanation for the high selectivity observed is that due to the selected substitution pattern and the perfect complementarity of polarity of each carbon-centred free radical with its opposed carbon–carbon double bond,[3] both cyclisations occur *almost synchronously*. In the event, the α-cyano radical resulting from the cyclopentanation process, which in



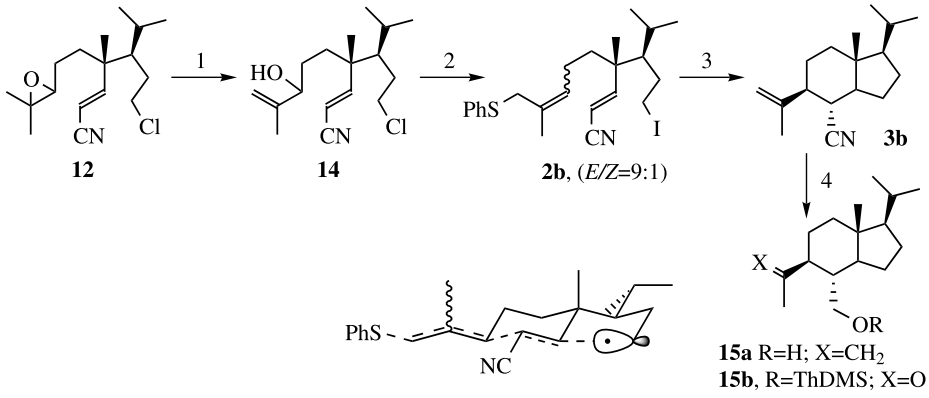
Scheme 3. *Reagents and conditions*: 1. (i) PhSCl (1 equiv.), CH_2Cl_2; −17°C, 10 min, then TBACN (3 equiv.), rt, overnight; (ii) column chromatography on silica gel (ether/hexane), then repetition twice of this sequence on recovered **9a** (91%, overall); 2. MCPBA (4 equiv.), Na_2CO_3 (8 equiv.), CH_2Cl_2; 0°C to rt, 5 h (98%); 3. SiO_2 (5 g/mmol), CH_2Cl_2; rt, 1 day; 4. (i) MCPBA (3 equiv.), $NaHCO_3$ (3 equiv.), CH_2Cl_2; 0°C to rt, 5 h (87%); (ii) KCN (1.5 equiv.), DMSO; rt, 5 h.

accordance with related observations[4] and in consonance with the Beckwith model[5] should proceed with the indicated geometry, is immediately trapped by the allylic residue with no possibility of inverting its configuration (Scheme 4).[6]

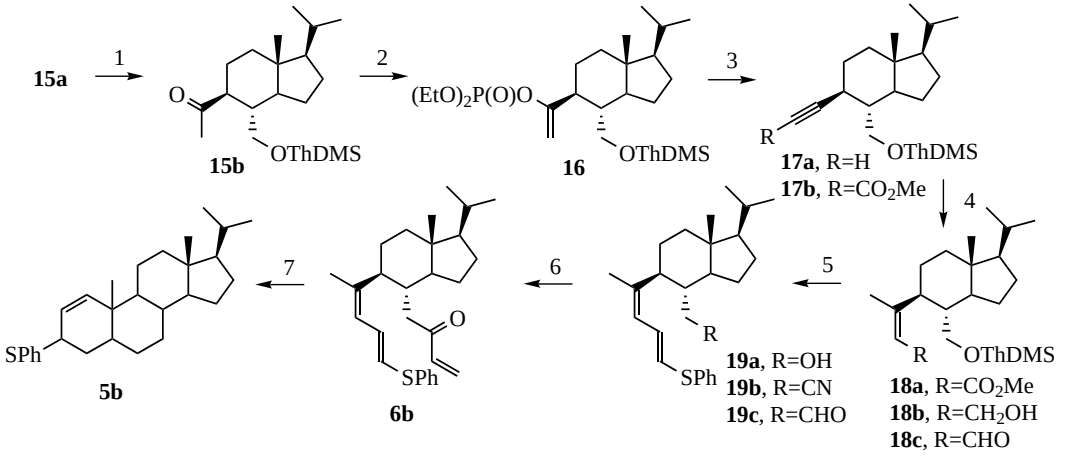
The conversion of the alcohol **15a** into a steroid compound was then examined (Scheme 5).

As described previously in related examples,[1b] **15a** was first protected as a thexyldimethylsilyl (ThDMS) *O*-derivative and ozonolysed to furnish **15b**. Trapping the kinetic lithio enolate of this ketone by diethyl chlorophosphate and reacting the resulting enol phosphate **16** with excess LDA gave the acetylenic derivative **17a**. Lithiation of **17a** (BuLi), and ensuing condensation with methyl chloroformate furnished the ester **17b**, then converted into the *Z* ester **18a** by methylcupration. Treatment of **18a** by excess DIBAH and oxidation of the resulting alcohol **18b** to the aldehyde **18c** with nickel peroxide was followed by condensation with diethyl phenylthiomethylphosphonate and treatment with TBAF to deliver the dienylsulfide **19a** as a mixture of diastereomers ($E/Z=4/1$; NMR). Homologation of this alcohol by tosylation and cyanation furnished the nitrile **19b**, which was then reduced (DIBAH) to the aldehyde **19c**. Finally, condensation of **19c** with vinylmagnesium bromide and ensuing IBX oxidation of the resulting crude product gave the labile ketone **6b**.

The thermal cyclisation of this trienyl derivative to **5b** was examined by heating a dilute toluene-d_8 solution of



Scheme 4. *Reagents and conditions*: 1. (i) Al(O-*i*-prop)$_3$ (3 equiv.), toluene; reflux, 29 h (98%); 2. (i) $SOCl_2$ (2 equiv.), ether; 0°C, 3 h; (ii) PhSLi (1 equiv.), DMF; 0°C to rt, 3 h; (iii) NaI (10 equiv.), butanone; reflux, 5 h (67% overall, from **14**); 3. $Bu_3SnSnBu_3$ (2.1 equiv.), benzene, 300 W Sunlight lamp; reflux, 3 days (75%); 4. (i) DIBAH (1 equiv.), CH_2Cl_2; −78°C, 3 h (96%); (ii) $NaBH_4$, EtOH; rt, 3 h (68%).



Scheme 5. *Reagents and conditions*: 1. (i) ThDMSCl (3 equiv.), imidazole (3 equiv.), DMF; rt, 4 h (78%); (ii) O_3/O_2, CH_2Cl_2/MeOH; −78°C, 20 min, then Me_2S (3.5 equiv.), −78°C to rt, 3 h (85%); 2. LDA (2 equiv.), THF; −78°C, 1 h, then $(EtO)_2P(O)Cl$ (1.5 equiv.), −78°C to rt, overnight (92%); 3. (i) LDA (4 equiv.), THF; −78°C, 2 h (92%); (ii) BuLi (1.2 equiv.), MeOC(O)Cl (1.2 equiv.), THF; −78°C, 30 min, then rt, 2 h (90%); 4. (i) CuI (3 equiv.), MeLi (5.6 equiv.), ether; 0 to −78°C, 10 min, then **17b** (1.2 M, in THF), −60°C, 3 days, then excess MeOH, −78 to 0°C, 30 min (70%); (ii) DIBAH (2.5 equiv.), CH_2Cl_2; −78°C, 3 h (78%); (iii) NiO_2 (8 equiv.), benzene; rt, 2 h (85%); 5. (i) $PhSCH(Li)P(O)(OEt)_2$ (1.8 equiv.), THF; rt, 1.5 h (86%); (ii) TBAF (2 equiv.), THF; rt, 15 h (89%); (iii) tosyl chloride (1.5 equiv.), pyridine; 0°C, overnight (85%); (iv) NaCN (1.8 equiv.), DMSO; 80°C, 2 h (78%); (v) DIBAH (1.2 equiv.), CH_2Cl_2; −78°C, 2 h (80%); 6. (i) 1 M (in THF) vinylmagnesium bromide, THF; −78°C, 2 h; (ii) IBX (1.8 equiv.), DMSO; rt, 1 h (69%); 7. toluene-d_8; 145°C, overnight.

6b at 145°C in a sealed NMR tube. Though the stereochemical fate of this reaction could not be clearly established, the close similarity of the signals, especially those corresponding to an allylic phenylsulfide residue, displayed by the newly-formed product with those previously observed in a strongly related case indicates that the expected isomerisation process occurs effectively.

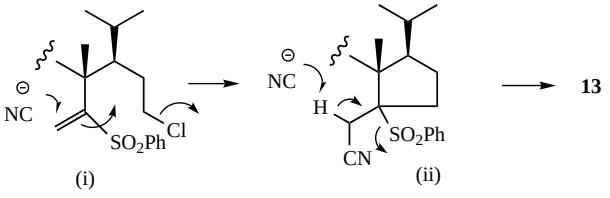
In conclusion, the possibility of accessing to the brassinolide skeleton from **1** has been verified but it is clear that the number of steps required by the **3b**–**6b** conversion is at present much too high to make this approach to brassinosteroids of real practical value. However, given the ease with which the iodonitrile **2b** could be obtained in a reduced number of steps from nerol **7** and, furthermore, the perfect stereoselectivity with which this iodide cyclises to **3b**, such a hydrindane derivative remains a powerful intermediate for constructing the A-B-C-D ring system of brassinosteroids. Accordingly, efforts are now being paid both to apply these results to the preparation of homochiral **3a** and to shorten significantly the **3a**–**5** conversion.[7]

Acknowledgements

Thanks are due to 'Le Ministère de la Recherche et de la Technologie' for a grant (to O.T.).

References

1. (a) Temmem, O.; Uguen, D.; De Cian, A.; Gruber, N. *Tetrahedron Lett*. **2002**, *43*, 3175–3179; (b) Temmem, O.; Uguen, D.; De Cian, A.; Gruber, N. *Tetrahedron Lett*. **2002**, *43*, 3169–3173 and references therein.
2. Presumably formed via the intermediates (i) and (ii) as indicated:



3. Giese, B.; Meixner, J. *Chem. Ber*. **1981**, *114*, 3073–3100 and references cited therein.
4. For a related approach to hydrindane derivatives, see: (a) Takahashi, T.; Tomida, S.; Sakamoto, Y.; Yamada, H. *J. Org. Chem*. **1997**, *62*, 1912–1913; (b) Takahashi, T.; Tomida, S.; Doi, T. *Synlett* **1999**, 644–645.
5. (a) Beckwith, A. L. J.; Ingold, K. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4; (b) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100.
6. *Protocol for the free-radical cyclisation process*: In a 1 litre round-bottomed flask equipped with a condenser connected to an argon/vacuum line, a solution of the iodide **2b** (4.1 g; 8.1 mmol) and hexa-*n*-butylditin (8.6 ml; 2 equiv.) in benzene (850 ml) was thoroughly degassed (three 'freeze and thaw' cycles), then filled with argon before being brought to reflux by irradiating the flask with a 300 W Sunlight lamp. After 3 days, TLC analysis indicated traces of unreacted starting iodide. Additional tin reagent was added (1 ml; 0.12 equiv.) and the irradiation continued overnight. After cooling, the solvent was removed in vacuo and the residue was triturated in acetonitrile. The resulting solution was stirred with KF (3 g) for 3 h at rt, the resulting mixture being filtered on a pad of basic alumina. The solvents were then removed in vacuo and the residue was chromatographed on silica gel (ether/hexane) to afford the nitrile **3b** as a colourless oil (1.5 g; 75%).
7. *Selected data*: **9a**: (mixture of diastereomers): C, H (%): 70.26, 11.07 (calcd: 70.43, 10.71); **12**: C, H (%): 68.23, 9.31 (calcd: 68.55, 9.47); **13**: ^{1}H NMR: 0.87 (d, $J=7$ Hz, 3H), 0.98 (d, $J=7$ Hz, 3H), 1.01 (s, 3H), 1.24 (s, 3H), 1.31 (s, 3H), 1.35–2.03 (m, 8H), 2.34–2.52 (m, 1H), 2.65 (t, $J=6$ Hz, 1H), 2.61–2.88 (m, 1H), 5.08–5.2 (m, 1H); **14**: ^{1}H NMR: 0.085 (d, $J=7$ Hz, 3H), 0.98 (d, $J=7$ Hz, 3H), 1.01 (s, 3H), 1.28–1.91 (m, 7H), 1.7 (s, 3H), 1.96–2.13 (m, 1H), 3.46–3.57 (m, 2H), 3.97–4.03 (m, 1H), 4.86 (d, $J=1.4$ Hz, 1H), 4.84 (s, 1H), 5.23 (d, $J=16.7$ Hz, 1H), 6.66 (d, $J=16.7$ Hz, 1H); ^{13}C NMR: 17.9, 18.9, 19.1, 21.6, 26.8, 29.3, 29.7, 29.9, 34.6, 45.3, 48.9, 75.9, 98.7, 111.2, 117.8, 147.3, 163.4; **2b**: ^{1}H NMR (major diastereomer): 0.83 (d, $J=7$ Hz, 3H), 0.97 (s, 3H), 0.99 (d, $J=7$ Hz, 3H), 1.17–1.42 (m, 3H), 1.7 (s, 3H), 1.68–2.05 (m, 5H), 3–3.26 (m, 2H), 3.47 (s, 2H), 5.07 (t, $J=8.6$ Hz, 1H), 5.17 (d, $J=16.8$ Hz, 1H), 6.62 (d, $J=16.8$ Hz, 1H), 7.19–7.39 (m, 3H); ^{13}C NMR (major diastereomer): 7.3, 15.3, 18.4, 18.8, 22.9, 25.5, 26.7, 31.4, 38.5, 44.3, 45.6, 52.9, 99.6, 117.8, 126.5, 128, 128.7, 131.1, 131.4, 136.1, 163.2; **3b**: ^{1}H NMR: 0.7 (s, 3H), 0.85 (d, $J=6.5$ Hz, 3H), 0.92 (d, $J=6.5$ Hz, 3H), 0.98–1.06 (m, 1H), 1.12–1.32 (m, 3H), 1.37–2.04 (m, 10H), 2.09–2.23 (m, 2H), 4.88–4.98 (m, 2H); ^{13}C NMR: 11.5, 19.9, 22.5, 23.1, 25.2, 27.2, 27.7, 31.1, 33.2, 38.7, 42.3, 49.1, 51.5, 57.8, 112.6, 121.3, 145.5; **15a**: ^{1}H NMR (400 MHz): 0.72 (s, 3H), 0.88 (d, $J=6.5$ Hz, 3H), 0.96 (d, $J=6.5$ Hz, 3H), 1.05 (m, 1H), 1.17–1.35 (m, 4H), 1.42–1.74 (m, 5H), 1.75 (s, 3H), 1.83–1.89 (m, 1H), 1.92–1.97 (m, 1H), 2.1–2.18 (dd, $J=4$, 11.5 Hz, 1H), 3.51 (dd, $J=4.7$, 11.2 Hz, 1H), 3.62 (dd, $J=2.9$, 11.2 Hz, 1H), 4.79 (s, 1H), 4.85 (d, $J=1.7$ Hz); ^{13}C NMR (100 MHz): 12.3, 19.4, 22.9, 23.5, 24.9, 28.5, 28.7, 31.6, 40.1, 41.2, 43.2, 49.9, 51.1, 58.5, 65.1, 111.7, 150.5; **18a**: ^{1}H NMR (400 MHz): –0.02 (s, 3H), 0 (s, 3H), 0.8 (s, 6H), 0.86 (d, $J=6.6$ Hz and d, $J=$ 6.8 Hz, 6H), 0.94 (d, $J=6.6$ Hz, 3H), 0.98–1.06 (m, 1H), 1.11–1.39 (m, 5H), 1.43–1.88 (m, in which s at 1.86, 11H), 1.9–1.96 (m, 1H), 3.37–3.38 (m, 2H), 3.65 (s, 3H), 3.84 (s, 1H); ^{13}C NMR (100 MHz): –3.5, –3.4, 12.3, 18.9, 20.6, 21.3, 22.9, 23.6, 25.1, 25.5, 25.8, 27.7, 28.7, 31.4, 34.6, 39.7, 40.6, 42.1, 43, 51, 58.4, 64.7, 117, 164.6, 166.9; (***Z***,***E***)-**19c**: ^{1}H NMR: 0.74 (s, 3H), 0.85 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=6.6$ Hz, 3H), 1.03–2.22 (m, 14H), 2.24–2.44 (m, 2H), 5.98 (d, $J=11$ Hz, 1H), 6.27 (d, $J=14.7$ Hz, 1H), 6.7 (dd, $J=11$, 14 Hz, 1H), 7.17–7.4 (m, 5H), 9.71–9.72 (m, 1H). Excepted as otherwise stated, ^{1}H and ^{13}C NMR at 200 and 50 MHz, respectively, in $CDCl_3$. The results presented in this letter are taken in part from the thesis dissertation of Olivier Temmem (Strasbourg, December 2000).