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Efficient dehydrocyanation of hindered 1-substituted olefins

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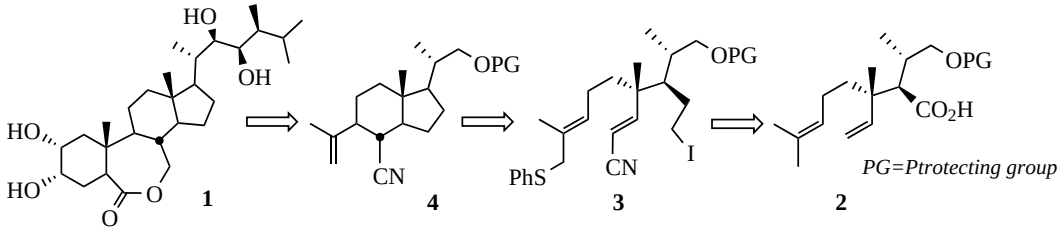
Abstract—The chlorosulfides **7** which formed quantitatively by reaction of olefins **5** with PhSCl under neutral conditions could be converted into the unsaturated nitriles **6** in good yields by sequential treatment with alkaline cyanides and MCPBA, a similar result being observed by reversing this order.

With the aim of synthesising the plant-growth promotor brassinolide **1** according to the approach summarised in Scheme 1, we have previously shown that using appropriate conditions the acid **2** could be obtained with an acceptable stereoselectivity by Ireland–Claisen rearrangement of a neryl ester. Accordingly, our next concern was to elaborate the acid **2** to the compound **3**, a potential precursor of the perhydrindane **4**.[1]

Due to the presence of two differently-substituted carbon–carbon bonds in the structure **2** and, moreover, to the neohexenyl-like substitution of the less-substituted one, the cumbersome step of this planned conversion would undoubtedly be the implementation of a cyano group at the terminus of the vinyl residue. We describe in this letter how this problem can be solved in the case of the model olefins **5a**–**c**, the application of the results of this study to the **2**–**4** conversion being reported in an accompanying letter.

Examination of the literature revealed that straightforward conversion of a 1-alkene into the corresponding α,β-unsaturated nitrile could be performed using either of the two methods summarised in Scheme 2.[2]

However, investigation of these procedures with neohexene **5a** to form **6a** proved disappointing. Whereas attempted cross-metathesis of **5a** with acrylonitrile under recently-described conditions[2b] gave only the homocoupling product of the electrophilic partner, its treatment with the Caserio reagent, then KCN and HBF_4 and ensuing oxidative elimination as described by Trost[2c] produced complex mixtures of rearranged products, probably a result of the acidic conditions required. This led us to consider the condensation of **5a** with PhSCl as a possible means of mediating the planned dehydrocyanation process, with the hope being as indicated that the chlorosulfide **7a**, claimed to be the kinetic product of this reaction, could be transformed into **8a** by treatment with cyanide under non-acidic



Scheme 1.

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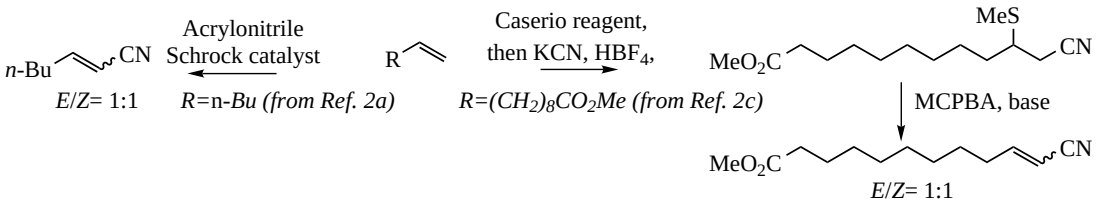


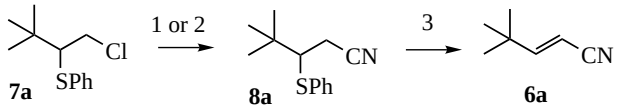
Scheme 2.

conditions (Scheme 3).[3] In the event, a subsequent oxidative elimination reaction would provide **6a**.

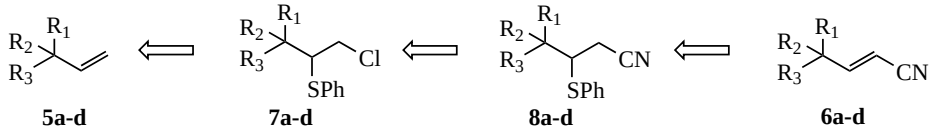
Treating **5a** with freshly distilled PhSCl at ca −10°C in CH_2Cl_2 as described[3] resulted in the formation of a chlorosulfide having NMR features similar to those reported for **7a**. Confirmation of this structure was secured by treatment of this sulfide with excess MCPBA to obtain a crystalline sulfone to which the structure **9a** was assigned by X-ray analysis (Scheme 4).[4] Furthermore, treatment of **9a** by DBU gave the sulfone **10a**, conclusively identified by NMR analysis.

Additional evidence for the structure **7a** came from the observation of a partial conversion of **7a** into the isomeric chlorosulfide **11** on attempted purification by column chromatography, an isomerisation which was rendered quantitative by stirring **7a** with silica gel in CH_2Cl_2 overnight at rt. Oxidation of this rearranged product with MCPBA gave a chlorosulfone having the structure **12** as clearly established by treatment with DBU and NMR analysis of the unsaturated sulfone **13** thus produced.

Cyanation of the chlorosulfide **7a** was first tried by using standard conditions (KCN, DMSO; Scheme 5). Reacting the cyanosulfide **8a** thus formed with excess MCPBA under basic conditions (Na_2CO_3) gave the desired nitrile **6a** in good yield (80% overall, from **7a**) and with a perfect *E* selectivity (NMR).

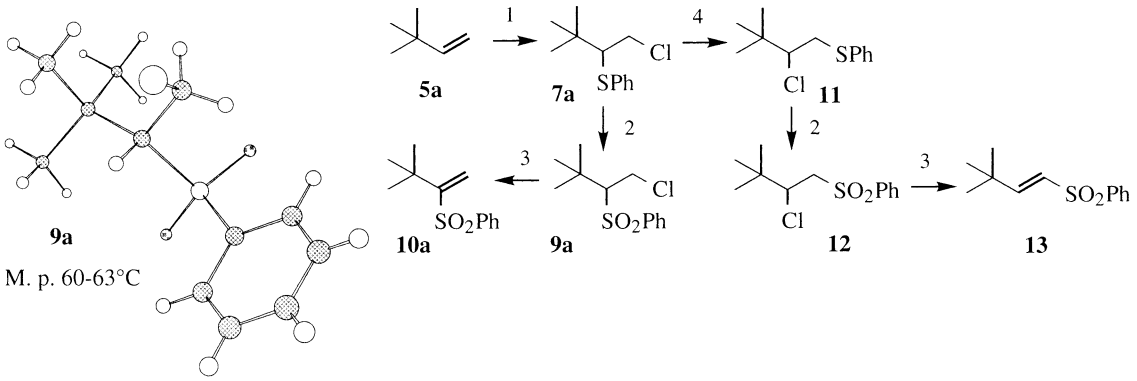


Scheme 5. *Reagents and conditions*: 1. KCN (5 equiv.), DMSO (5 ml/mmol); rt, 12 h (81%); 2. *n*-Bu_4NCN (5 equiv.), CH_2Cl_2 (4 ml/mmol); rt, overnight (86%); 3. MCPBA (3 equiv.), Na_2CO_3 (6 equiv.), CH_2Cl_2 (10 ml/mmol); 0°C, 15 min, then rt, 5 h (99%).



5a, $R_1=R_2=R_2=Me$
5b, $R_1=R_2=Me$; $R_3=CH_2OTBDMS$
5c, $R_1=R_2=Me$; $R_3=CH_2CO_2Me$
5d, $R_1=Me$; R_2, $R_3=CH_2OC(Me_2)OCH_2$

Scheme 3.

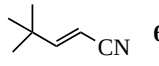
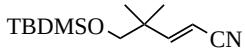
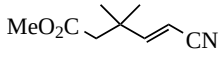
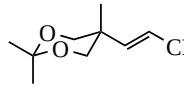


Scheme 4. *Reagents and conditions*: 1. PhSCl (1 equiv.), CH_2Cl_2 (1.3 ml/mmol); −10°C, 10 min, then rt, 10 min; 2. MCPBA (3 equiv.), $NaHCO_3$ (6 equiv.), CH_2Cl_2 (3 ml/mmol); 0°C to rt, 3 h; 3. DBU (1.5 equiv.), CH_2Cl_2 (2 ml/mmol); rt, 5 h; 4. silica gel (3 g/mmol), CH_2Cl_2 (10 ml/mmol); rt, overnight (100%).

The possibility of performing both the chlorosulfanylation and the cyanation steps in the same flask was next examined. To this end excess *N*-tetrabutylammonium cyanide (TBACN) was added to the chlorosulfanylation mixture, without isolation of the chlorosulfide **7a**. After a few hours, removal of unreacted TBACN with water, followed by treatment of the formed cyanosulfide **8a** with the MCPBA/Na_2CO_3 reagent afforded the pure nitrile **6a** in 81% yield after purification on silica gel. This two-step process proved capable of being extended to more elaborated substrates (Table 1).[5]

A minor shortcoming of this otherwise satisfactory dehydrocyanation process came into light when we noticed that treatment by TBACN of pure **7d** induced partial reversion of the sulfanylation process as evidenced by the detection in GLC of PhSCN alongside **5d**. Efforts to suppress this side reaction proved ineffective, which led us to examine the condensation of the chlorosulfone **9a** with cyanides since no reversion to the olefin **5a** had been expected in this case. A few vinylic sulfones have been shown to give the corresponding nitriles by treatment with KCN: due to the basicity of this reagent, the cyanosulfone thus formed eliminating a sulfinate to give the corresponding α,β-unsaturated nitrile.[6] It thus could be hoped that **9a** would react with excess cyanide, acting both as a base and a nucleophile, to give successively the vinylic sulfone **10a** (and a chloride ion), the cyanosulfone **14**, and then the nitrile **6a**.

Table 1. Dehydrocyanation of the olefins **5a–d** by the 'two-step process'

Starting Olefin	Product (Yield)*
5a	 **6a** (81 %)
5b	 **6b** (80 %)
5c	 **6c** (67 %)
5d	 **6d** (80 %)

* Overall, from compound **5**

That basic elimination of a sulfinate ion in **14** would proceed with the desired *E* selectivity was confirmed by first reacting **10a** with NaCN in presence of AcOH (Scheme 6). Treatment of the resulting cyanosulfone **14** with *t*-BuOK in THF gave the pure (NMR) nitrile **6a** (99%; 87% overall).

The chlorosulfone **9a** was next reacted with KCN (twofold excess) in DMSO and after 24 h the nitrile **6a** was isolated in high yield.[7] Attempts to use a protic solvent proved less rewarding however. In *t*-BuOH, with added crown ether as recommended,[6a] the 3:7 mixture of the vinylic sulfone **10a** and the cyanosulfone **14** which formed initially (Table 2, entry 2) evoluted to give ultimately a 4:1 mixture of **14** and **6a** (entry 3). Interestingly, the same 4:1 mixture resulted by submitting **10a** to these conditions (entry 4), lending credence to the elimination–addition pathway presented above.

In conclusion, one-carbon homologation of hindered olefins into the corresponding α,β-unsaturated nitriles has been realised by a very simple procedure which usefully complements methods based on prior degradation of olefins into aldehydes and ensuing cyanomethylenation condensations.[8]

Table 2. Incidence of solvent conditions on the **9a–6a** conversion

	Substrate	Conditions[a]	Product composition (%)
Entry 1	**9a**	A, 24 h	**6a** (95)
Entry 2	**9a**	B, 4 h	**10a** (30), 14 (70)
Entry 3	**9a**	B, 15 h	**14** (80), **6a** (20)
Entry 4	**10a**	B, 15 h	**14** (80), **6a** (20)

[a] Conditions A: KCN (2 equiv.) in DMSO (2 ml/mmol); rt. Conditions B: KCN (10 equiv.), 18-crown-6 (0.1 equiv.) in *t*-BuOH (2 ml/mmol); reflux.

Acknowledgements

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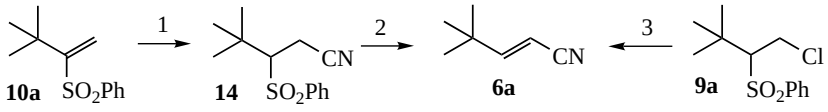

Scheme 6. *Reagents and conditions*: 1. NaCN (20 equiv.), 15-crown-5 (0.2 equiv.), AcOH (1.2 equiv.), H_2O (1 ml/mmol), CH_2Cl_2 (1 ml/mmol); rt, 15 h (88%); 2. *t*-BuOK (1 equiv.), THF (5 ml/mmol); rt, 0 min (99%); 3. KCN (2 equiv.), DMSO; rt, 1 day (95%).

References

1. Temmem, O.; Uguen, D.; De Cian, A.; Gruber, N. *Tetrahedron Lett*. **2002**, *43*, 3169–3173.
2. (a) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc*. **1995**, *117*, 5162–5163; (b) Blanco, O. M.; Castedo, L. *Synthesis* **1999**, 557–558; (c) Trost, B. M.; Shibata, T.; Martin, S. *J. Am. Chem. Soc*. **1982**, *104*, 3228–3230.
3. Mueller, W. H.; Butler, P. E. *J. Am. Chem. Soc*. **1968**, *90*, 2075–2081. For reviews on the chlorosulfanylation of olefins and *i. a.* the reactivity of halosulfides with nucleophilic reagents, see for instance: (a) Lucchini, V.; Modena, G.; Pasquato, L. *Gazz. Chim. Ital*. **1997**, 127, 178–188; (b) Koval, I. V. *Russian Chem. Rev*. **1995**, *64*, 731–751.
4. Crystal data of **9a**: $C_{12}H_{17}O_2SCl$, MW = 260.79, triclinic, space group $P\bar{1}$, $a = 8.003(2)$, $b = 7.971(2)$, $c = 21.018(6)$ Å, $\alpha = 91.93(2)$, $\beta = 99.11(2)$, $\gamma = 90.22(2)°$, $V = 1323(1)$ Å^3, $Z = 4$, $D_{calcd} = 1.31$ g cm^{-3}, μ(Mo Kα) = 0.422 mm^{-1}. Data were collected using a Nonius Mach3 diffractometer, graphite monochromated Mo Kα radiation ($\lambda = 0.7173$ Å) at room temperature. 4978 reflections were collected using a crystal of 0.35×0.30×0.20 mm^3. The structure was solved using direct methods and refined with 3076 reflections having $I > 3\sigma(I)$. Hydrogen atoms were introduced as fixed contributors at their computed coordinates (d(C–H) = 0.95 Å, B(H) = 1.3). Full matrix refinements against $|F|$. Final results: $R(F) = 0.041$ Å, $R_w(F) = 0.063$, GOF = 1.27, largest peak in final difference = 0.45 e Å^{-3}. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, for compound **9a**. 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).
5. In all cases, the chlorosulfide was independently characterised and treated successively with MCPBA, then DBU, and each intermediate being identified by NMR. *Protocol for the two-step process*: (N.B. All operations conducted under an argon atmosphere and in using well-dried glassware) Freshly prepared, and distilled (34°C at 1τ), PhSCl (1 equiv.) was added by syringe as a 3.5 M CH_2Cl_2 solution (2.86 ml) to a cooled (ice/methanol) and well-stirred solution of the olefin **5a** (10 mmol) in the same solvent (10 ml). After the initial yellow coloration had discharged (10 min), the resulting colourless solution was further stirred at rt for 10 min. Subsequently a solution of TBACN (13.4 g; 5 equiv.) in CH_2Cl_2 (40 ml) was added. The resulting mixture was stirred overnight at rt. The solvent was removed in vacuo and the residue taken up in ether (500 ml). After washing with water (4×100 ml), and drying ($MgSO_4$), the solvents were removed in vacuo to give the cyanosulfide **8a** as a pale yellow oil, which was immediately diluted with CH_2Cl_2 (100 ml). After cooling (ice/methanol), Na_2CO_3 (6.5 g; 6 equiv.) and 80% MCPBA (6.5 g; 3 equiv.) were sequentially added. After 15 min, the cooling bath was removed and the mixture was stirred at rt (5 h), before being poured into 0.25 M Na_2SO_3 (200 ml). The aqueous layer was extracted with CH_2Cl_2 (3×100 ml) and the combined organic phases were washed with saturated $NaHCO_3$ (100 ml), brine (100 ml), and dried ($MgSO_4$). The oily residue left by evaporation of the solvents was then purified by chromatography on silica gel (hexane/ether) to give pure nitrile **6a** (882 mg; 81%).
6. (a) Taber, D. F.; Saleh, S. A. *J. Org. Chem*. **1981**, *46*, 4817–4819; (b) Bailey, P. L.; Jackson, R. F. W. *Tetrahedron Lett*. **1991**, *32*, 3119–3122.
7. *Protocol for the oxidation–cyanation process*: $NaHCO_3$ (5 g; 6 equiv.) was added with stirring to a solution of the chlorosulfide **7a** prepared as described previously.[5] After dilution with CH_2Cl_2 (30 ml), and cooling (ice/methanol), 80% MCPBA (6.5 g; 3 equiv.) was added and the resulting mixture was stirred for 3 h at rt, then poured into 0.25 M $Na_2S_2O_3$. The resulting two-phase system was worked-up as described above for the **8a**–**6a** conversion to afford the crystalline chlorosulfone **9a** (2.55 g; 98%). KCN (1.63 g; 2 equiv.) was added to a stirred solution of **9a** (1.3 g; 5 mmol) in DMSO (10 ml). After 24 h stirring at rt, the reaction mixture was diluted with ether (300 ml), then washed with water (4×50 ml), brine (2×50 ml), and dried ($MgSO_4$). The residue left by evaporation of the solvents was chromatographed on silica gel (pentane/ether). After removal of the solvents, the crude nitrile **6a** was further purified by bulb-to-bulb distillation to give **6a** as a pale yellow liquid (491 mg; 90%). It is worth noting that 2-*t*-butylsuccinonitrile, which was detected (NMR) in the crude product and removed during the purification steps, was the only isolated product (99%) using KCN in larger excess (5 equiv.). Selected data: **7a**: ^{1}H NMR: 1.13 (s, 9H), 3.13 (dd, $J = 5$, 7 Hz, 1H), 3.65 (dd, $J = 7$, 12 Hz, 1H), 3.93 (dd, $J = 5$, 12 Hz, 1H), 7.21–7.36 (m, 3H), 7.48–7.53 (m, 2H); ^{13}C NMR: 28.4, 36.2, 46.3, 64.3, 126.9, 129.2, 131.6, 136.5; **11**: ^{1}H NMR: 1.04 (s, 9H), 3.06 (dd, $J = 10.5$, 14 Hz, 1H), 3.45 (dd, $J = 2.5$, 14 Hz, 1H), 3.79 (dd, $J = 2.5$, 10.5 Hz, 1H), 7.22–7.42 (m, 5H); ^{13}C NMR: 26.6, 36.2, 39.4, 72.6, 126.7, 129, 130.3, 136.5; **9a**: Mp 60–63°C (hexane/ether); ^{1}H NMR: 1.3 (s, 9H), 3.22 (t, $J = 4$ Hz, 1H), 3.7 (dd, $J = 4$, 13 Hz, 1H), 3.78 (dd, $J = 4$, 13 Hz, 1H), 7.57–7.7 (m, 3H), 7.9–7.95 (m, 2H); ^{13}C NMR: 28.9, 36.5, 39.6, 76.1, 126.5, 129.4, 133.8, 140.4; **12**: ^{1}H NMR: 0.98 (s, 9H), 3.49 (dd, $J = 8.5$, 15 Hz, 1H), 3.58 (dd, $J = 2$, 15 Hz, 1H), 4.05 (dd, $J = 2$, 8.5 Hz, 1H), 7.52–7.7 (m, 3H), 7.9–8 (m, 2H); **10a**: Mp 136–139°C (hexane/ether); ^{1}H NMR: 1.22 (s, 9H), 5.96 (d, $J = 1.1$ Hz, 1H), 6.28 (d, $J = 1.1$ Hz, 1H), 6.28 (d, $J = 1.1$ Hz, 1H), 6.28 (d, $J = 1.1$ Hz, 1H), 7.5–7.6 (m, 3H), 7.84–7.9 (m, 2H); ^{13}C NMR: 30.3, 36.5, 124.9, 127.7, 129.1, 133.1, 140.4, 159.5; **13**: Mp 54–56°C (hexane/ether); ^{1}H NMR: 1.08 (s, 9H), 6.26 (d, $J = 15$ Hz, 1H), 6.99 (d, $J = 15$ Hz, 1H), 7.5–7.61 (m, 3H), 7.84–7.89 (m, 2H); ^{13}C NMR: 28.3, 34.1, 126.6, 127.5, 129.2, 133.2, 140.8, 156.4; **8a**: ^{1}H NMR: 1.13 (s, 9H), 2.62 (dd, $J = 7.3$, 17.1 Hz, 1H), 2.75 (dd, $J = 5.3$, 17.1 Hz, 1H), 3.07 (dd, $J = 5.3$, 7.3 Hz, 1H), 7.26–7.38 (m, 3H), 7.52–7.57 (m, 2H); **14**: ^{1}H NMR: 1.29 (s, 9H), 2.67 (dd, $J = 5.5$, 18 Hz, 1H), 2.82 (dd, $J = 5.5$, 18 Hz, 1H), 3.22 (t, $J = 5.5$, 1H), 7.57–7.75 (m, 3H), 7.91–7.96 (m, 2H); ^{13}C NMR: 26.9, 39.6, 70.7, 76.2, 121.3, 128.5, 129.4, 133.8, 140.4; **6a**: ^{1}H NMR: 1.08 (s, 9H), 5.23 (d, $J = 16.5$ Hz, 1H), 6.63 (d, $J = 16.5$ Hz, 1H); **6b**: ^{1}H NMR: 0.03 (s, 6H), 0.89 (s, 9H), 1.02 (s, 6H), 3.35 (s, 2H), 5.29 (d, $J = 16.8$ Hz, 1H), 6.75 (d, $J = 16.8$ Hz, 1H); **6c**: ^{1}H NMR: 1.21 (s, 6H), 2.37 (s, 2H), 3.66 (s, 3H), 5.29 (d, $J = 16.5$ Hz, 1H), 6.82 (d, $J = 16.5$ Hz, 1H); **6d**: ^{1}H NMR: 0.99 (s, 3H), 1.4 (s, 3H), 1.45 (s, 3H), 3.49–3.93 (m, 4H), 5.58 (d, $J = 16$ Hz, 1H), 6.89 (d, $J = 16$ Hz, 1H); **8b**: ^{1}H NMR: 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.04 (s, 3H), 1.07 (s, 3H), 2.67 (dd, $J = 7.3$, 17.1 Hz, 1H), 3.4 (dd,

$J=5.2$, 7.3 Hz, 1H, plus d, $J=10$ Hz, 1H), 3.65 (d, $J=10$ Hz, 1H), 3.7 (dd, $J=5.2$, 17.1 Hz, 1H), 7.25 (m, 3H), 7.51–7.57 (m, 2H); **8d**: ^{1}H NMR: 0.96 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 2.65–2.71 (m, 1H), 3.49–3.93 (m, 6H), 7.21–7.35 (m, 3H), 7.4–7.45 (m, 2H); **9b**: Mp 87–88°C; ^{1}H NMR: 0.08 (s, 3H), 0.1 (s, 3H), 0.91 (s, 9H), 1.19 (s, 3H), 1.31 (s, 3H), 3.49 (d, $J=10$ Hz, 1H), 3.7 (t, $J=4$ Hz, 1H), 3.82 (s, 2H), 3.83–3.87 (m, 1H), 7.52–7.66 (m, 3H), 7.91–8.01 (m, 2H); ^{13}C NMR: −5.8, −5.7, 18, 22.8, 23.7, 25.7, 39.2, 41.5, 69.9, 71, 128.4, 129.2, 133.9, 139; **9c**: Mp 87–89°C; ^{1}H NMR: 1.33 (s, 3H), 1.4 (s, 3H), 2.41 (d, $J=1.15$ Hz, 1H), 3.44 (d, $J=15$ Hz, 1H), 3.7 (dd, $J=5$, 11 Hz, 1H), 3.72 (s, 3H), 3.85 (dd, $J=5$, 11 Hz, 1H), 4.38 (t, $J=5$ Hz, 1H), 7.53–7.73 (m, 3H), 7.91–8.01 (m, 2H); ^{13}C NMR: 25.1, 27.4, 37.4, 38.9, 44.4, 51.2, 69.8, 128, 129.1, 133.6, 139.9, 172.2; **9d**: Mp 88–92°C; ^{1}H NMR: 1.3 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 3.56–3.79 (m, 3H), 3.94–4.04 (m, 3H), 4.55 (dd, $J=2.8$, 12.1 Hz, 1H), 7.57–7.69 (m, 3H), 7.95–8 (m, 2H); **10b**: ^{1}H NMR: 0 (s, 6H), 0.84 (s, 9H), 1.13 (s, 6H), 3.53 (s, 2H), 6 (s, 1H), 6.4 (s, 1H), 7.52–7.66 (m, 3H), 7.91–8.01 (m, 2H); ^{13}C NMR: −5.5, 18.2, 24.7, 25.7, 41.7, 70.1, 127.6, 127.7, 129, 133, 141.8, 155.1; **10c**: ^{1}H NMR: 1.33 (s, 6H), 2.78 (s, 2H), 3.72 (s, 3H), 5.96 (d, $J=1.6$ Hz, 1H), 6.25 (d, $J=1.6$ Hz), 7.51–7.61 (m, 3H), 7.86–7.91 (m, 2H); ^{13}C NMR: 26.3, 38.4, 45.1, 51.2, 126.4, 127.9, 129.1, 133.3, 141.4, 156.9, 172.2; **10d**: ^{1}H NMR: 1.23 (s, 3H), 1.29 (s, 3H), 1.38 (s, 3H), 3.6 (d, $J=11.9$ Hz, 2H), 4.14 (d, $J=11.9$ Hz, 2H), 6.26 (d, $J=1.4$ Hz, 1H), 6.47 (d, $J=1.4$ Hz, 1H), 7.53–7.62 (m, 3H), 7.85–7.9 (m, 2H); ^{13}C NMR: 20.1, 23.2, 24.2, 38.7, 87.8, 98.1, 127.8, 128.4, 129.2, 133.4, 141.2, 153.6. All ^{1}H and ^{13}C NMR spectra 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).

8. D'sa, B. A.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961–3967 and references cited therein.