Consecutive Reactions with Sulfoximines: Straightforward Synthesis of Substituted 5,5-Spiroketals

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Abstract: An efficient sysnthesis of 5,5-spiroketals, i.e. 1,6-dioxaspiro[4.4]nonane derivatives, is described from 2-(sulfonimidoylmethylene)tetrahydrofurans involving a consecutive epoxide opening / oxa-Michael spiroketalization sequence. This methodology was applied to the very direct synthesis of chalcogran, a beetle pheromone.

Key words: Sulfoximine, 5,5-spiroketals, consecutive reaction, chalcogran.

Introduction

Spiroketals are structural subunits found in many biologically active natural products originated from a variety of sources including marine, vegetal, insect or bacterial sources.[1] These molecules display a broad range of biological activities such as antibiotic,[2] antifungal,[3] anti-HIV,[4] or could find applications in cancer therapy.[5] The spiroketal moiety is often the primary pharmacophore in these molecules, and in some cases, simplified analogs retaining essentially the spiroketal moiety have shown comparable biological activity with the natural products.[6] Because of their pharmaceutical interest, spiroketals have become popular synthetic targets and a variety of methods are now available to access these useful compounds. The most common strategy relies on the cyclization of a linear α,ω-dihydroxyketone or a synthetic equivalent,[7] and transition metal-catalyzed spiroketalizations of unsaturated α,ω-diols were also described.[8] Other useful strategies involve the iodoetherification of ene ketals[9] or a hetero-Diels–Alder cycloaddition between an α,β-unsaturated carbonyl compound and an α-methylene tetrahydropyran or -furan.[10] Although these methods are effective and reliable, the access to the spiroketalization precursor(s) usually requires several steps.

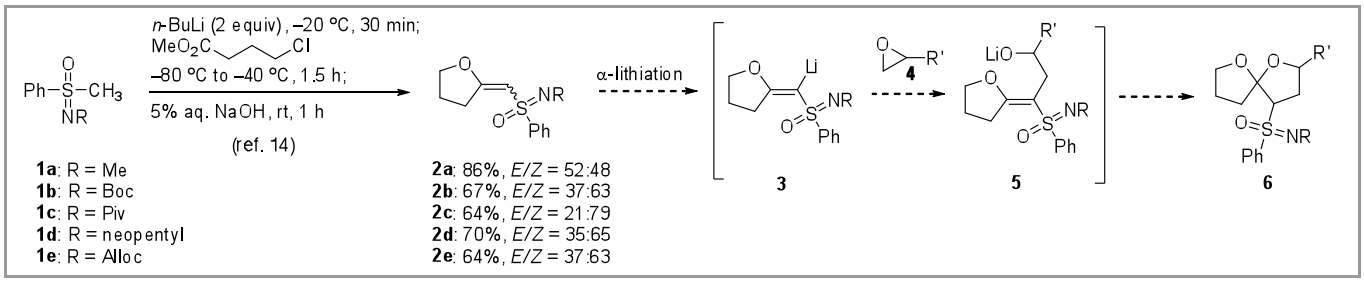
An important focus for contemporary organic synthesis is economy.[11] Indeed, the efficiency of a synthetic sequence is more than ever determined by issues of brevity and sustainability, as witnessed by the tremendous efforts currently directed at the development of multiple bond-forming[12] and catalytic chemical processes.[13] The efficiency of a chemical synthesis can be measured by parameters such as selectivity and overall yield, of course, but also by its raw material, time, human resources and energy requirements, as well as the toxicity and hazard of the chemicals and the protocols involved. It is thus now recognized that the step count is one of the most important criteria when evaluating the efficiency of a synthesis.

In connection with our continuous interest in the development of novel multiple bond-forming transformations,[14] we recently reported the chemo- and regioselective synthesis of 2-(sulfonimidoylmethylene)tetrahydrofurans **2** by a consecutive acylation/S_N reaction of sulfoximines **1** with α,ω-haloesters (Scheme 1).[15] The use of chiral sulfoximines in asymmetric synthesis is well established,[16] and changing the nature of the substituent on the nitrogen atom can easily modify their steric and electronic demand. In addition these chiral auxiliaries can be removed, recycled or even exploited in further transformations. We report herein an efficient transformation of compounds **2** into 5,5-spiroketals (*i.e.* 1,6-dioxaspiro[4.4]nonane derivatives) in a single operation, and its application to the synthesis of chalcogran, a beetle pheromone.

Results and discussion

We surmised that compounds **2** could be transformed into 5,5-spiroketals **6** in a single operation *via* a domino epoxide ring opening / oxa-Michael spiroketalization sequence involving successively the lithiated olefin **3** and the lithium alcoholate **5** (Scheme 1). It should be noted that related stepwise strategies have been explored from α-lithiated vinylsulfones.[17,18]

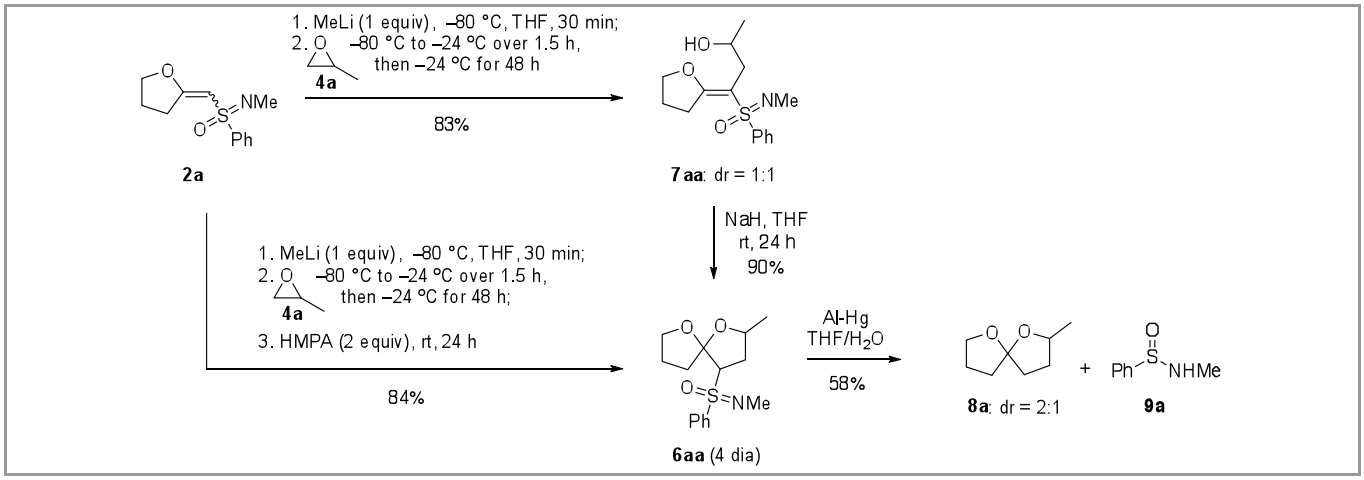
In order to validate this strategy, the diastereomeric mixture of *(E)*- and *(Z)*-*N*-methyl-2-(sulfonimidoylmethylene)tetrahydrofuran **2a** was first treated with methyl lithium at low temperature to produce mainly the lithiated intermediate *(E)*-**3a** (R = Me).[15b] Subsequent addition of 2-methyloxirane (**4a**, R' = Me) led to the opening of the epoxide; however the resulting alcoholate did not undergo the expected spiroketalization, and following hydrolysis, the alcohol **7aa** was instead isolated in good yield (Scheme 2). Surprisingly, the use of various Lewis acids ($BF_3{\cdot}OEt_2$, Et_2AlCl, $InCl_3$)[19] resulted in lower yields of product and/or decomposition of the starting



Scheme 1

material. Prolonged reaction time and/or elevation of the reaction temperature did not allow the expected domino spiroketalization. Alternatively, the desired intramolecular oxa-Michael cyclization could be achieved by treatment of **7aa** with sodium hydride at room temperature and afforded the targeted 5,5-spiroketal **6aa** in good yield but as an inseparable mixture of at least four diastereomers (Scheme 2). In a separate experiment, a single diastereomer of **7aa** was submitted to the same conditions to provide **6aa** as a 1:1 mixture of two diastereomers in similar yield, probing some degree of diastereoselectivity in the oxa-Michael cyclization step (2 diastereomers obtained over 4 possible). In order to facilitate analysis, the chiral sulfonimidoyl group was reductively cleaved from **6aa** with aluminum-mercury amalgam to afford the 5,5-spiroketal **8a** (dr = 2:1) in 58% yield with the corresponding sulfinamide **9a**.

Having shown the feasibility of each individual step, we had yet to demonstrate that a domino or consecutive sequence[12] could also be viable. Indeed, after *in situ* generation of the lithium alcoholate **5aa** (R = R' = Me) from **2a**, addition of HMPA [hexamethylphosphoramide] promoted the desired spiroketalization in good yield, thus allowing the synthesis of **6aa** directly from **2a** by a consecutive reaction. As in the two steps protocol, the sulfonimidoyl group was cleaved to yield **8a** as the same mixture of diastereomers, but the consecutive protocol was found more efficient (Scheme 2).



Scheme 2 Stepwise and consecutive synthesis of 5,5-spiroketal **6aa**.

Scope and limits of this spiroketalization reaction were examined by changing the nature of the substituents on both the oxirane and the sulfinimidoyl group. Results are summarized in Table 1. The consecutive reaction proved to be very general affording the 5,5-spiroketal products **6** in good yields, and functionalized substituents could be introduced *via* the epoxide **4** (entries 7, 9 and 10). It seems that in every case a fraction of the product **8** decomposed during the removal of the sulfonimidoyl group and/or during the purification by flash chromatography on silica gel as evidenced by the systematically lower yields of spiroketal **8** compared to sulfinamide **9**. The configuration of the double bond in substrate **2a** had no significant impact on the reaction outcome (compare entries 1 and 2, see ref 15b) as well as the nature of the nitrogen substituent R (compare entries 3 and 4, and 5 and 6). Unfortunately, the diastereomeric ratio of the sulfonimidoyl-free 5,5-spiroketals **8** was very close to 1:1 in all cases, except for **8a** and **8f** (dr = 2:1). Actually, the lack of diastereoselectivity observed in this approach to 5,5-spiroketals is a common feature to many syntheses of such systems. Indeed, it is well known that 5,6- and 6,6-spiroketals can equilibrate due to an anomeric effect combined with the minimization of steric interactions. However, in the case of 5,5-spiroketals, the anomeric effect is severely diminished due to the lack of well-defined

axial and equatorial positions. Although the stereoselective formation of 5,5-spiroketals has been described in few examples,[20] epimers at the spiranic carbon atom typically equilibrate to nearly 1:1 mixtures in these systems, especially for lightly substituted compounds.[21] Overall, the above methodology allows a straightforward and efficient synthetic access to 5,5-spiroketals **6** from sulfoximines **1** in only two steps, each step being a consecutive reaction. It is worth to note that the present approach to 2-substituted-1,6-dioxaspiro[4.4]nonane derivatives **8** has allowed one of the most direct synthesis of (±)-chalcogran (**8b**), the principal component of the aggregation pheromone of the bark beetle *Pityogenes chalcographus* (L.), a pest of the Norway spruce.[22]

Table 1 Consecutive reaction for the synthesis of 5,5-spiroketals **6** and **8**[a]

Entry	Substrate	Epoxide **4**	Yield of **6** (%)[b]	Yield of **8** (%)[c]
1	**2a** (*E*/*Z* = 52:48)	**4a**: R' = Me	**6aa**: 84 (75)	**8a**: 58 (84)
2	(*Z*)-**2a**	**4a**: R' = Me	**6aa**: 72	**8a**: 55 (84)
3	**2a** (*E*/*Z* = 52:48)	**4b**: R' = Et	**6ab**: 85 (81)	**8b**: 69 (85)
4	**2b** (*E*/*Z* = 37:63)	**4b**: R' = Et	**6bb**: 71	**8b**: 70 (81)
5	**2a** (*E*/*Z* = 52:48)	**4c**: R' = *n*Bu	**6ac**: 80	**8c**: 72 (83)
6	**2b** (*E*/*Z* = 37:63)	**4c**: R' = *n*Bu	**6bc**: 75	**8c**: 69 (79)
7	**2a** (*E*/*Z* = 52:48)	**4d**: R' = CH_2OPh	**6ad**: 61	**8d**: 85 (86)
8	**2a** (*E*/*Z* = 52:48)	**4e**: R' = Ph	**6ae**: 68	**8e**: 50 (69)
9	**2a** (*E*/*Z* = 52:48)	**4f**: R' = 3-butenyl	**6af**: 79 (70)	**8f**: 85 (86)
10	**2a** (*E*/*Z* = 52:48)	**4g**: R' = vinyl	**6ag**: 69 (68)	**8g**: 65 (79)

[a]All reactions were performed under the conditions described in Scheme 2.
[b]Yields of the consecutive reaction determined by isolation of the mixture of diastereomers after flash chromatography on silica gel. The yields in brackets are for the two steps sequence *via* **7** (when determined).
[c]Compounds **8** were obtained as nearly 1:1 mixtures of two diastereomers, except for **8a** and **8f** (dr = 2:1). The yields have been determined based on isolated product after flash chromatography on silica gel. The yields for **9a** (or **9b** for entries 4 and 6) are in brackets.

Conclusion

In conclusion, we have developed a simple and rapid methodology for the synthesis of substituted 5,5-spiroketals based on two successive anionic consecutive reactions from sulfoximines **1**. Indeed, a consecutive acylation/S_N2 reaction allowed the synthesis of a variety of 2-(sulfonimidoylmethylene)tetrahydrofurans **2**, which in turn were the substrates of a consecutive epoxide ring opening/oxa-Michael reaction affording 5,5-spiroketals **6**. However, and as it is the case in most alternative syntheses of 5,5-spiroketals moities, the stereochemistry of the spiro carbon atom could not be controlled. The methodology was applied to the synthesis of (±)-chalcogran (**8b**), a naturally occurring pheromone.

Experimental section

All reagents were obtained from commercial sources and used as supplied unless otherwise stated. HMPA was dried over CaH_2 and distilled under an argon atmosphere. Anhydrous diethyl ether, THF and dichloromethane were obtained from a solvent purification system. The reactions were monitored by TLC, which were performed on Merck 60 F254 plates. Flash chromatography was performed with Macherey-Nagel 70-230 mesh silica gel. NMR data were recorded on a Bruker Avance 300 spectrometer in $CDCl_3$ and chemical shifts (δ) are given in ppm relative to the residual non-deutered solvent signal for ^{1}H NMR ($CHCl_3$: 7.26 ppm), and relative to the deutered solvent signal for ^{13}C NMR ($CDCl_3$: 77.0 ppm); coupling constants (J) are in Hertz, and the classical abbreviations are used to describe the signal multiplicity. Mass spectra were recorded on a Bruker Esquire 6000 spectrometer equipped with an electrospray ionization source and an ion trap detector. High-resolution mass spectra were obtained from the Spectropole (http://www.spectropole.u-3mrs.fr/). Melting points (mp) were determined with a Büchi Melting-point B-450 apparatus and were not corrected. FTIR spectra were recorded on a Perkin-Elmer 1600 spectrometer.

General procedure for the synthesis of compounds 6 *via* 7

To a stirred solution of **2** (3 mmol) in THF (18 mL) under an argon atmosphere at –80 °C was added an ethereal solution of MeLi (3 mmol) and stirring was continued for 30 min. Epoxide **4** (4.5 to 6 mmol) was then added and temperature was gradually increased (over 1.5 h) to –24 °C and kept at this temperature for 48 h. The reaction mixture was then hydrolyzed with a saturated NH_4Cl solution, and the organic layer was separated. The aqueous medium was extracted twice with diethyl ether, and the combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, filtered and concentrated to give the crude product. The crude product was purified by flash chromatography on silica gel eluted with ethyl acetate in petroleum ether to give **7** as an inseparable mixture of two diastereomers. The two diastereomers of **7aa** were partially separated (90% diastereomeric purity).

To a stirred suspension of NaH (1.2 mmol) in THF (6 mL) under an argon atmosphere was added a solution of **7** (1 mmol) in THF (6 mL) at room temperature.

Stirring was continued for 24 h, the reaction mixture was then hydrolyzed with a saturated NH_4Cl solution, and the organic layer was separated. The aqueous medium was extracted twice with diethyl ether, and the combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, filtered and concentrated to give the crude product. The crude product was purified by flash chromatography on silica gel eluted with ethyl acetate in petroleum ether to give **6** as an inseparable mixture of four isomers. From **7aa** (90% diastereomeric purity), **6aa** was obtained as a mixture of two isomers, which were separated (90% diastereomeric purity).

General procedure for the synthesis of compounds 6 by the consecutive reaction

To a stirred solution of **2** (1 mmol) in THF (6 mL) at –80 °C under an argon atmosphere was added an ethereal solution of MeLi (1 mmol) and stirring was continued for 30 min. Epoxide **4** (2 mmol) was then added and temperature was gradually increased (over 1.5 h) to –24 °C and kept at this temperature for 48 h. The mixture was then allowed to warm room temperature and HMPA (2 mmol) was added and stirring was continued for 24 h. The reaction mixture was then hydrolyzed with a saturated NH_4Cl solution, and the organic layer was separated. The aqueous medium was extracted twice with diethyl ether, and the combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, filtered and concentrated to give the crude product. The crude product was purified by flash chromatography on silica gel eluted with ethyl acetate in petroleum ether to give **6** as an inseparable mixture of four isomers identical to the mixture obtained by the two-steps protocol.

7aa (1st eluted diastereomer): viscous liquid; IR (neat) 2985, 1615, 1434, 1226, 1141 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, J = 6.2 Hz, 3H), 1.97-2.19 (m, 2H), 2.25-2.33 (m, 1H), 2.56-2.64 (m, 1H), 2.67 (s, 3H), 2.92-3.03 (m, 1H), 3.28-3.39 (m, 1H), 3.89-3.95 (m, 1H), 4.11-4.23 (m, 2H), 6.40 (broad s, 1H), 7.51-7.57 (m, 3H), 7.80-7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.0, 24.5, 28.9, 29.7, 37.2, 67.1, 71.6, 109.6, 128.5, 129.2, 132.1, 140.2, 169.8; HRMS (ESI+) *m/z* found: $[M+H]^+$ 296.1314, $C_{15}H_{22}NO_3S^+$ requires 296.1315.

(2nd eluted diastereomer): viscous liquid; IR (neat) 2994, 1615, 1435, 1227, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, J = 6.2 Hz, 3H), 1.94-2.11 (m, 3H), 2.62 (s, 3H), 2.69-2.85 (m, 2H), 3.14-3.25 (m, 1H), 3.92-3.42 (m, 1H), 4.09-4.22 (m, 2H), 5.93 (broad s, 1H), 7.48-7.59 (m, 3H), 7.84-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 24.5, 28.8, 29.5, 35.6, 66.8, 71.5, 109.2, 128.4, 129.0 (2C), 131.9 (2C), 140.6, 169.9; HRMS (ESI+) *m/z* found: $[M+H]^+$ 296.1313, $C_{15}H_{22}NO_3S^+$ requires 296.1315.

6aa (1st eluted diastereomer): viscous liquid; IR (neat) 2953, 2861, 1435, 1243, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, J = 6.3 Hz, 3H), 1.77-1.85 (m, 1H), 1.97-2.34 (m, 4H), 2.60-2.64 (m, 1H), 2.68 (s, 3H), 3.69-4.10 (m, 4H), 7.53-7.60 (m, 3H), 7.83-7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.7, 24.5, 29.2, 32.6, 36.4, 66.5, 71.1, 71.4, 113.2, 129.2, 129.6, 132.8, 138.3; HRMS (ESI+) *m/z* found: $[M+H]^+$ 296.1317, $C_{15}H_{22}NO_3S^+$ requires 296.1315.

(2nd eluted diastereomer): viscous liquid; IR (neat) 2850, 2847, 1435, 1235, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, J = 6.3 Hz, 3H), 1.19-1.27 (m, 1H), 1.70-1.77 (m, 1H), 1.98-2.05 (m, 3H), 2.40-2.50 (m, 1H), 2.62 (s, 3H), 3.83-3.94 (m, 3H), 4.07-4.16 (m, 1H), 7.48-7.54 (m, 3H), 7.76-7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 24.3, 29.2, 33.9, 34.6, 66.2, 68.3, 71.0, 112.7, 128.7, 130.4, 132.6, 136.8; HRMS (ESI+) *m/z* found: $[M+H]^+$ 296.1318, $C_{15}H_{22}NO_3S^+$ requires 296.1315.

General procedure for the synthesis of 8

Aluminium-mercury amalgam was prepared by adding small pieces of aluminium foil (1.0 g) to a solution of $HgCl_2$ (1.0 g) in water (50 mL). The mixture was stirred for one minute and filtered. The resulting material was washed rapidly with water and THF, and then added to a stirred solution of **6** (1.3 mmol) in 7:1 THF/H_2O (40 mL). Stirring was continued for 2 h whereupon the mixture was filtered through celite, and the filtrate was extracted twice with CH_2Cl_2. The combined organic layers were washed once with small amount of water, dried with anhydrous magnesium sulfate, filtered and concentrated to give the crude product. The crude product was purified by flash chromatography on silica gel eluted with increasing amounts of ethyl acetate in petroleum ether to give the spiroketal **8** as a mixture of two diastereomers followed by the sulfinamide **9**.

Compounds **8a**,[21a,b] **8b**,[23] and **8f**[21b] exhibited physical and spectroscopic properties identical with previously reported data, except for optical rotations when applicable.

8c (dr = 1:1): liquid; IR (neat) 2933, 2853, 1447, 1333, 1144, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83-0.88 (m, 6H), 1.19-1.75 (m, 14H), 1.82-2.12 (m, 14H), 3.78-4.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.6, 22.7, 24.3, 24.5, 27.9, 28.1, 30.0, 30.8, 34.6, 34.8, 35.1, 35.3, 35.7, 36.9, 66.6, 66.8, 78.1, 80.0, 114.2, 114.4; HRMS (ESI+) *m/z* found: $[M+H]^+$ 185.1535, $C_{11}H_{21}O_2^+$ requires 185.1536.

8d (dr = 1:1): liquid; IR (neat) 2931, 1446, 1328, 1139, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81-2.32 (m, 16H), 3.83-4.15 (m, 8H), 4.43-4.53 (m, 2H), 6.93-6.98 (m, 6H), 7.26-7.32 (m, 4H); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 24.3, 24.5, 27.1, 27.8, 34.2, 34.3, 34.6, 35.0, 66.8, 67.1, 70.1, 72.1, 76.1, 114.5, 115.0, 115.3, 120.6, 120.7, 129.2, 129.3, 158.8, 158.9; HRMS (ESI+) *m/z* found: $[M+H]^+$ 235.1330, $C_{14}H_{19}O_3^+$ requires 235.1329.

8e (dr = 1:1): liquid; IR (neat) 2925, 1482, 1335, 1148, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86-2.39 (m, 16H), 3.93-4.16 (m, 4H), 5.00-5.17 (m, 2H), 7.24-7.30 (m, 3H), 7.33-7.38 (m, 5H), 7.43-7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4, 24.6, 33.7, 34.7, 34.8, 35.0, 35.1, 36.3, 67.0, 67.1, 79.5, 82.1, 114.9, 115.2, 125.7, 126.2, 127.1, 127.2, 128.2, 128.3, 143.0, 143.7; HRMS (ESI+) *m/z* found: $[M+H]^+$ 205.1205, $C_{13}H_{17}O_2^+$ requires 205.1223.

8g (dr = 1:1) liquid; IR (neat) 2920, 1631, 1447, 1335, 1011 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.3, 24.5, 30.8, 31.4, 34.3, 34.7, 35.0, 35.7, 66.9, 67.0, 78.8, 80.9, 115.1, 115.2, 138.8, 140.4; HRMS (ESI+) *m/z* found: $[M+H]^+$ 155.1066, $C_9H_{15}O_2^+$ requires 155.1067.

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Supporting Information for this article contains copies of ^1H and ^{13}C NMR spectra of all new compounds, and is available online at http://www.thieme-connect.de/ejournals/toc/synthesis.

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