CSIRO PUBLISHING

Rapid Communication

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2004**, *57*, 673–676

Concerning the Proposed Structure of (+)-Laurobtusol: Spectral Discrepancies with Synthetic, Racemic Stereoisomers

Joanne T. Blanchfield,[A] *Sharon Chow*,[A] *Paul V. Bernhardt*,[A] *Colin H. L. Kennard*,[A] *and William Kitching*[A,B]

[A] Department of Chemistry, School of Molecular and Microbial Sciences, University of Queensland, Brisbane QLD 4072, Australia.

[B] Author to whom correspondence should be addressed (e-mail: w.kitching@uq.edu.au).

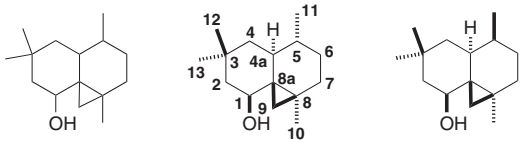
Laurobtusol, a minor metabolite from *Laurencia obtusa*, had been assigned constitution **1** and relative stereochemistry, **2**. However, several stereoisomers of this novel, cyclopropane-containing system **1** have now been synthesized and spectral correspondence between the synthesized isomers and laurobtusol is lacking.

Manuscript received: 25 February 2004.
Final version: 14 April 2004.

Investigation of the red alga *Laurencia obtusa* by Caccamese and coworkers[1] led to the isolation of a minor component, named laurobtusol, to which constitution **1** was assigned (Scheme 1) largely on the basis of 250 MHz NMR spectral data. This structure incorporates an unprecedented carbocyclic skeleton considered to arise from the α-humulene system.[1] The relative stereochemistry shown in **2** (slightly favoured over its 5-epimer **3**) was based on computational processing of the lanthanide-induced shifts in the ^{1}H NMR spectra and molecular mechanics calculations for the eight possible diastereomers. We now report the synthesis of a number of diastereomers of **1**, including **2** and **3**.[2]

The *syn* nature of the cyclopropylcarbinyl alcohol unit in **2** suggested a hydroxyl-directed cyclopropanation[3] of an allylic alcohol as the final step. The initial approach is shown in Scheme 2. All structures shown indicate relative configurations only.

Conjugate addition of Grignard reagent **5** to enone **4** (Scheme 2) provided a 1 : 1 diastereomeric mixture of enones **6**, and this was then converted to the diketones **7** by Wacker oxidation.[4] Intramolecular aldolization–dehydration of **7** afforded three inseparable enones **8**, **9**, and presumably **10** (5 : 5 : 1). Reduction with $LiAlH_4$ was highly stereoselective and the 5 : 5 : 1 mixture of **8**–**10** provided essentially the same proportions of allylic and homoallylic alcohols (the latter from **10**). The relative stereochemistry of the purified alcohols **11** and **12** was inconclusive from the NMR data, but those portrayed in Scheme 2 were confirmed by later comparisons with an alcohol of confirmed structure (X-ray crystal structure determination). Cyclopropanation of **11** and **12** with variants of the Simmons–Smith and samarium-based procedures[5,6] was very inefficient, and alternative methods by which to attain system **1** were investigated. Upon treatment with dimethylsulfoxonium methylide,[7] the α, β-enones

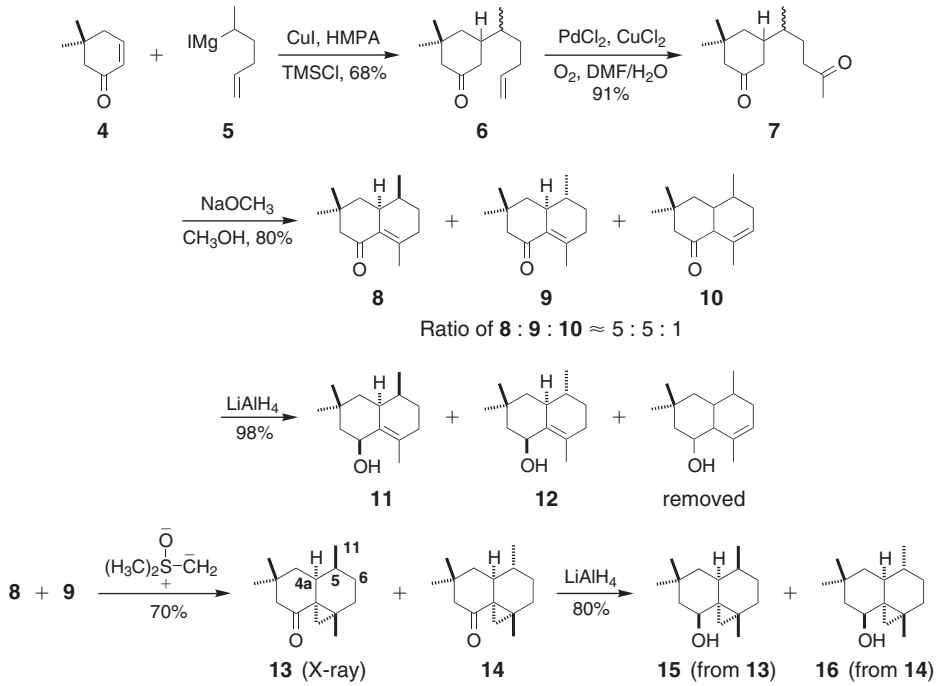


1 **2** **3**

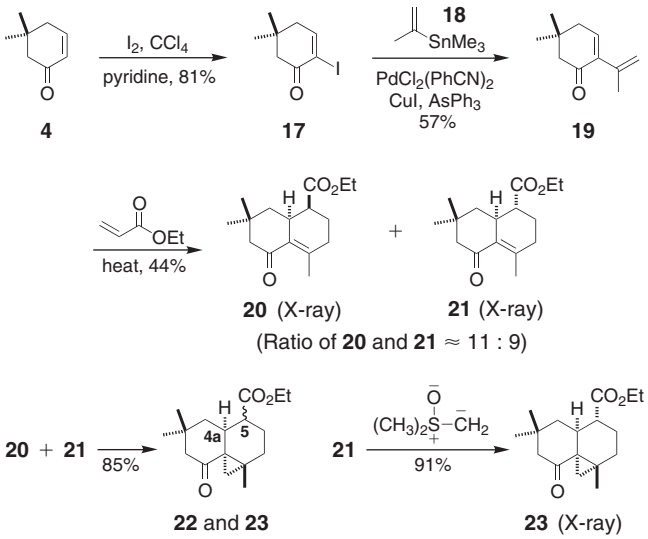
Scheme 1.

8 and **9** provided a 1 : 1 mixture of separable cyclopropyl ketones **13** and **14**, respectively (Scheme 2). X-Ray crystal structure determination of the crystalline isomer **13** confirmed a *cis* relationship between the cyclopropyl group and H4a; this was consistent with the NMR spectra, and confirmed that **14** was the C5-epimer of **13**. Both rings in **13** have chair-like geometries in the crystalline state, but ^{1}H and ^{13}C NMR studies indicate that in solution conformational flexing occurs with pronounced signal broadening of C1–3, C6, C8a, C9, C11, and H1. As judged by the sharp ^{13}C NMR signals, such flexing is not important for the non-crystalline ketone **14** in which the C11 methyl group is equatorial. Ketones **13** and **14** were reduced with high stereoselectivity by $LiAlH_4$ to the corresponding alcohols, which were separated and assigned structures **15** and **16**, respectively. The H1 resonances for **15** and **16** are located at δ 3.62 (apparent t, J 3.3 Hz) and δ 3.47 (t, J 3.0 Hz), respectively; this suggests that the alcohol groups are axial. However, the alcohol-bearing ring appears to favour a half-boat conformation which attenuates axial and equatorial differences. In laurobtusol (assigned structure **2**), H1 resonates at δ 3.90 (dd, J 11.4, 2.5 Hz) and displays a large axial–axial coupling;[1] this is consistent with an equatorial alcohol. The relative stereochemistry shown for **15** and **16** (see Scheme 2) was confirmed by their subsequent acquisition from an allylic alcohol precursor (see Scheme 4), the

 10.1071/CH04047 0004-9425/04/070673



Scheme 2. Synthesis of **15** and **16** by ylide addition.



Scheme 3. The Diels–Alder approach to esters **20** and **21**, and their dimethylsulfoxonium ylide cyclopropanation.

relative stereochemistry of which was established by X-ray crystal structure determination.

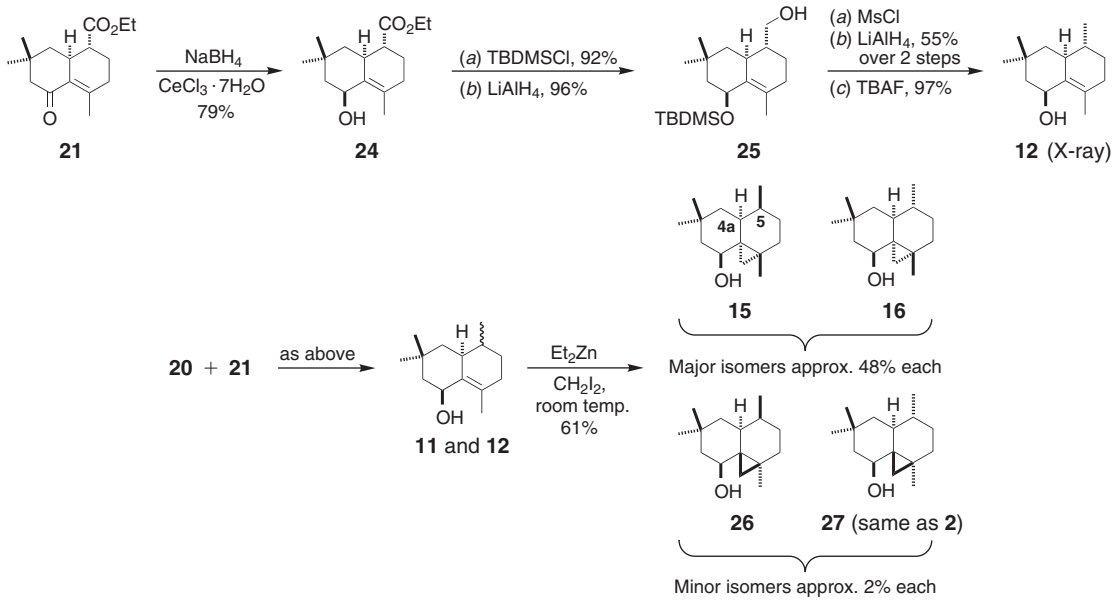
The ^{1}H and ^{13}C NMR and mass spectral data for **15** and **16**, which are representatives of system **1**, exhibit worrisome differences from the data for laurobtusol, even allowing for the stereochemical variations between **15**, **16**, and **2**. In view of this, a new approach was devised which would not only deliver the double bond ready for cyclopropanation, but possibly also superior stereochemcial control (about C4a and C5) and ease of structural definition.

Iodoketone **17**[8] was coupled with vinylstannane **18** to afford dienone **19**. Cycloaddition of ethyl acrylate proceeded with the desired regioselectivity to afford comparable amounts of separable esters **20** and **21** (ratio approximately 11 : 9), whose relative configurations were established by X-ray crystal structural determinations and NMR studies. This sequence is summarized in Scheme 3.

A mixture of ketoesters **20** and **21**, as well as **21** alone were cyclopropanated with dimethylsulfoxonium methylide to afford **22** and **23** (Scheme 3), respectively. The relative stereochemistry depicted was established by NMR studies, and in the case of **23** by an X-ray crystal structure determination. In both cases, that is, irrespective of the configuration of the ester, the cyclopropyl group was introduced *syn* to H4a. Therefore, neither **22** nor **23** possess the relative stereochemistry about the cyclopropyl centres as has been suggested for laurobtusol, and which is shown in **2**.

Ketoester **21** was transformed into monoprotected diol **25** as shown in Scheme 4, and then into allylic alcohol **12**, whose constitution and relative stereochemistry were established by NMR spectroscopy and X-ray crystal structure determination. Alcohol **12** possesses the bicyclic system and relative stereochemistry postulated for laurobtusol. If hydroxyl-directed *syn* cyclopropanation of this alcohol could be achieved, the favoured structure for laurobtusol, namely **2**, would be acquired.

Thus, the mixture of ketoesters **20** and **21** was processed as outlined above for **21** to give a roughly equal mixture of **11** and **12**, and reinvigorated efforts were made to cyclopropanate the two resultant products (and some derivatives). The best procedure incorporated the use of diethylzinc and methylene iodide at room temperature. GCMS and GCHRMS examinations of the product from **11** and **12** confirmed that four cyclopropyl carbinyl alcohols, $C_{15}H_{26}O$ ($M^{+\bullet}$ measured, GCHRMS, see Experimental for data) had been produced in a reasonable yield (61%), with two major (approximately 48% each) and two minor isomers (approximately 2% each) being present



Scheme 4. Conversion of esters **20** and **21** into the tricyclic cyclopropyl carbinyl alcohols, **15**, **16**, **26**, and **27**.

(Scheme 4). The surprisingly high facial selectively of this cyclopropanation and inconclusive HPLC separation of the minor isomers necessitated spectroscopic examination of the product mixture. Examinations on different GCMS systems (Brisbane and Hamburg) revealed that all four isomers exhibited mass spectra that were so similar that a common carbon framework was mandated. Slight differences in the relative intensities of the fragment ions (particularly m/z 125, 138, 165, 204, and 207, see ESI) suggested the pair-wise relationship shown in Scheme 4. However, it should be noted that all the mass spectra were different from that for laurobtusol, which was kindly provided to us by Professor Caccamese. Although some differences would be anticipated because of the different mass spectral operating conditions, the actual differences were more profound and could not reasonably be explained on this basis. In particular, the fragment ions at m/z 71, 150, 180, and 209, which were significant in the mass spectrum of laurobtusol, were of very low abundance or absent from the spectra of the synthesized isomers. The fragment ion at m/z 209 ($[M-13]^{+\bullet}$) for laurobtusol is particularly difficult to rationalize.

The high-field two-dimensional NMR data (750 MHz) for the major isomers uniquely defined the carbocyclic systems shown for **15** and **16**, and therefore, on the basis of spectroscopic arguments, also of **26** and **27**. The signals for the cyclopropyl protons H9, H1, and H4a were easily identified in each of the two major isomers (**15** and **16**). Moreover, the strong nOes displayed between these protons confirmed that the allylic alcohols **11** and **12** predominantly undergo *anti* cyclopropanation to give the relative stereochemistry shown. Modelling studies were consistent with this observed facial selectivity, although cyclopropanation of allylic alcohols is normally *syn* to the hydroxyl group.[3] As it was clear that the two major isomers were in fact **15** and **16** shown in Scheme 4, the minor isomers **26** and **27** were the most likely structures for laurobtusol. High-field (500 and 750 MHz) ^{1}H NMR spectra in both $CDCl_3$ and C_6D_6 detected high-field signals for the cyclopropyl methylene protons as AB or AX systems for all four isomers. Two major H1 signals (in **15** and **16**) were identified along with one minor signal, and all were triplets with $4.7 > J > 3.2$ Hz. The other minor H1 signal was not discernible, and was presumably masked by one of the major signals. Signals corresponding to C1 were also located in the ^{13}C NMR spectrum. Of the two major signals for **15** and **16**, one was noticeably broadened, and was therefore assigned to **15**. On the other hand, the sharper of the two minor signals was assigned to **27**, which depicts the preferred structure for laurobtusol. The other minor signal, which was expected to be relatively broad, was assigned to **26** (see ESI). A summary of these data is shown in Table 1. As can be seen, there is poor correspondence with the analogous data reported for laurobtusol.

Table 1. ^{1}H NMR shifts of H1 and H9 in the tricyclic systems 15, 16, 26, and 27, together with the analogous data for laurobtusol

Isomers	^{1}H NMR chemical shifts (δ, 750 MHz, $CDCl_3$)	
	H9	H1
15	0.40 (d, *J* 4.2) 0.38 (d, *J* 4.2)	3.62 (dd, *J* 6.3, 3.3)
16	0.39 (d, *J* 4.2) 0.27 (d, *J* 4.2)	3.47 (t, *J* 3.2)
26	A	B
27 (=**2**)	0.36 (d, *J* 4.2) 0.29 (d, *J* 4.2)	3.49 (br t)
Laurobtusol	0.79 (d, *J* 4.5) 0.10 (d, *J* 4.5)	3.90 (dd, *J* 11.4, 2.5)

[A] Overlapping with signals in the 0.40–0.38 region.
[B] Overlapping with the major isomers in the 3.62 region.

A further four diastereomers of system **1** could be generated by notional epimerization at C1 in **15**, **16**, **26**, and **27**. Such structures would be of substantially higher energy, and

are contraindicated by the analyses of chemical shifts in the doped spectra.[1] In addition, these diastereomers would be anticipated to exhibit mass spectra similar to those of **15**, **16**, **26**, and **27**. The question remains as to the correct structure of laurobtusol, but this determination would require the re-isolation of this material as none of the original sample remains.[9] Our efforts to deduce an alternative structure for laurobtusol, for example of the perhydroazulenoid type, have been unrewarding.

Experimental

*1a,4,6,6-Tetramethyldecahydrocyclopropa[*d*]naphthalene-8-ol **15**, **16**, **26**, and **27***

Diethylzinc (0.28 mL, 1.0 M in hexane) was slowly added to the allylic alcohol mixture **11** and **12** (20 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) at 0°C (ice bath).[10] After stirring for 5 min, CH_2I_2 (22 μL, 0.27 mmol) was added dropwise. The cloudy solution was stirred for 3 h while the reaction mixture was warmed gradually to room temperature. After the addition of diethyl ether (4 mL), the flask was re-cooled to 0°C and saturated NH_4Cl (2 mL) was added. The aqueous layer was separated and re-extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and subjected to column chromatography (alumina, 10% diethyl ether/hexane). On the basis of GCMS analysis, the product (13 mg, 61%) consisted of two major and two minor isomers.

Compound **15** (major isomer) (Found: $M^{+\bullet}$ 222.1974. $C_{15}H_{26}O$ requires $M^{+\bullet}$ 222.1984). δ_H (500 MHz) 3.62 (1H, dd, *J* 6.3, 3.3, H1), 1.72 (1H, dt, *J* 13.5, 4.1, H4a), 1.66 (2H, m, H7), 1.58 (1H, m, H2), 1.56 (1H, m, H4), 1.54 (1H, m, H5), 1.52 (1H, m, H2), 1.26 (2H, m, H6), 1.23 (3H, s, H10), 1.07 (1H, dd, *J* 12.8, 3.8, H4), 1.02 (3H, s, H13), 0.97 (3H, s, H12), 0.79 (3H, d, *J* 6.8, H11), 0.40 (1H, d, *J* 4.2, H9), 0.38 (1H, d, *J* 4.2, H9). δ_C (125 MHz) 74.0 (C1), 44.6 (C2), 39.1 (C8), 38.0 (C4a), 34.3 (C13), 30.3 (C8a), 29.5 (C3), 29.1 (C12), 28.8 (C5), 28.1 (C7), 26.7 (C6), 22.4 (C10), 21.6 (C9), 20.5 (C8), 15.6 (C11). *m*/*z* (EIMS) 222 (1%, $M^{+\bullet}$), 207 (2), 204 (7), 189 (9), 165 (15), 151 (13), 133 (13), 125 (83), 107 (31), 93 (36), 79 (36), 69 (38), 55 (68), 41 (100).

Compound **16** (major isomer) (Found: $M^{+\bullet}$ 222.1995. $C_{15}H_{26}O$ requires $M^{+\bullet}$ 222.1984). δ_H (500 MHz) 3.47 (1H, t, *J* 3.0, H1), 1.80 (1H, ddd, *J* 13.4, 4.0, 2.5, $H7_{eq}$), 1.69 (1H, m, H2), 1.58 (1H, m, $H7_{ax}$), 1.65 (1H, m, H4), 1.45 (1H, m, H2), 1.40 (1H, m, $H6_{ax}$), 1.25 (3H, s, H10), 1.17 (1H, m, H4a), 1.06 (3H, s, H13), 0.94 (3H, s, H12), 0.86 (1H, m, H6), 0.81 (3H, d, *J* 7.0, H11), 0.39 (1H, d, *J* 4.2, H9), 0.27 (1H, d, *J* 4.2, H9). δ_C (125 MHz) 76.7 (C1), 42.0 (C4a), 41.6 (C2), 40.9 (C4), 36.4 (C5), 34.2 (C13), 32.5 (C7), 31.0 (C12), 30.8 (C8a), 30.0 (C6), 28.5 (C3), 25.0 (C9), 23.0 (C8), 22.9 (C10), 21.1 (C11). *m*/*z* (EIMS) 222 (2%, $M^{+\bullet}$), 207 (3), 204 (5), 189 (8), 165 (19), 151 (12), 133 (11), 125 (95), 107 (35), 93 (36), 79 (35), 69 (38), 55 (75), 41 (100).

Compounds **26/27** (minor isomer), see Table 1 for key NMR data (Found: $M^{+\bullet}$ 222.1967. $C_{15}H_{26}O$ requires $M^{+\bullet}$ 222.1984). *m*/*z* (EIMS) 222 (1%, $M^{+\bullet}$), 207 (3), 204 (8), 189 (7), 165 (52), 151 (13), 138 (22), 125 (45), 107 (30), 93 (36), 79 (31), 69 (35), 55 (93), 41 (100).

Compounds **27/26** (minor isomer), see Table 1 for key NMR data (Found: $M^{+\bullet}$ 222.1990. $C_{15}H_{26}O$ requires $M^{+\bullet}$ 222.1984). *m*/*z* (EIMS) 222 (5%, $M^{+\bullet}$), 207 (13), 204 (4), 189 (10), 165 (75), 151 (20), 138 (41), 125 (60), 107 (42), 93 (40), 79 (39), 69 (40), 55 (67), 41 (100).

Accessory Materials

The following material is available from the author or, until July 2009, the *Australian Journal of Chemistry*: general experimental procedures; a GC trace showing isomers **15**, **16**, **26**, and **27** and their EIMS; the mass spectrum of (natural) laurobtusol (courtesy of Professor S. Caccamese); ORTEP diagrams of compounds **13**, **20**, **21**, **23**, and **12**; ^1H and ^{13}C NMR spectral traces of (major) isomer **15** showing signal broadening phenomena; the 100 MHz ^{13}C NMR spectrum of the mixture **15**, **16**, **26**, and **27**; the 125 MHz ^{13}C NMR spectrum (C_6D_6) of the mixture **15**, **16**, **26**, and **27** in the region of C1; the 750 MHz ^1H NMR spectrum of **15**, **16**, **26**, and **27** in the high-field region (for C_6D_6 solvent) showing AX patterns for the cyclopropyl methylene groups; and spectral, analytical, and physical data of some key intermediates.

Acknowledgments

The authors are deeply indebted to Professors S. Caccamese and P. Neri, Universitá di Catania, Italy, for their friendly and cooperative exchanges of information, and for the copies of NMR and mass spectra of laurobtusol, to Professor J. C. Braekman of the Université Libre de Bruxelles, Belgium, for the mass spectrum of africanol, and to Professor Charette, Université de Montréal, Canada, for comments on cyclopropanation procedures. The GCHRMS of **15**, **16**, **26**, and **27** were very kindly obtained by Dr Stefan Franke and Professor Dr Wittko Francke of the Institute for Organic Chemistry, University of Hamburg, Germany, to whom we are most grateful.

References

[1] S. Caccamese, V. Amico, P. Neri, M. Foti, *Tetrahedron* **1991**, *47*, 10101. doi:10.1016/S0040-4020(01)96059-4

[2] Some of this work is described in the following theses: (*a*) J. Blanchfield, *Ph.D. Thesis* **1996** (University of Queensland: Brisbane).
(*b*) S. Chow, *Ph.D. Thesis* **2004** (University of Queensland: Brisbane), submitted.
Professor Ho (National Chiao Tung University, Taiwan) briefly outlined in 1998 a proposed route to laurobtusol resembling our conjugate addition–aldolization procedure shown in Scheme 2. T. L. Ho, S. T. Yeh, *216th ACS National Meeting* **1998** (ACS: Boston, MA).
Professor Ho informed W.K. in March 2003 that his group had acquired two stereoisomers of laurobtusol, and a possible intermediate that could be converted into racemic laurobtusol. None of this work has been published.

[3] S. Winstein, J. Sonnenberg, L. de Vries, *J. Am. Chem. Soc.* **1961**, *83*, 3235.

[4] J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett.* **1976**, 2975, and references therein. doi:10.1016/S0040-4039(01)85504-0

[5] S. E. Denmark, J. P. Edwards, *J. Org. Chem.* **1991**, *56*, 6974.

[6] G. A. Molander, S. C. Harring, *J. Org. Chem.* **1989**, *54*, 3525.

[7] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353.

[8] C. R. Johnson, J. P. Adams, M. P. Braun, C. B. W. Senanayake, *Tetrahedron Lett.* **1992**, *33*, 919. doi:10.1016/S0040-4039(00)91576-4

[9] S. Caccamese, unpublished results.

[10] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53. doi:10.1016/0040-4020(68)89007-6