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Stereospecific construction of three contiguous quaternary carbon atoms. Synthesis of (±)-3-methoxythaps-8-ene

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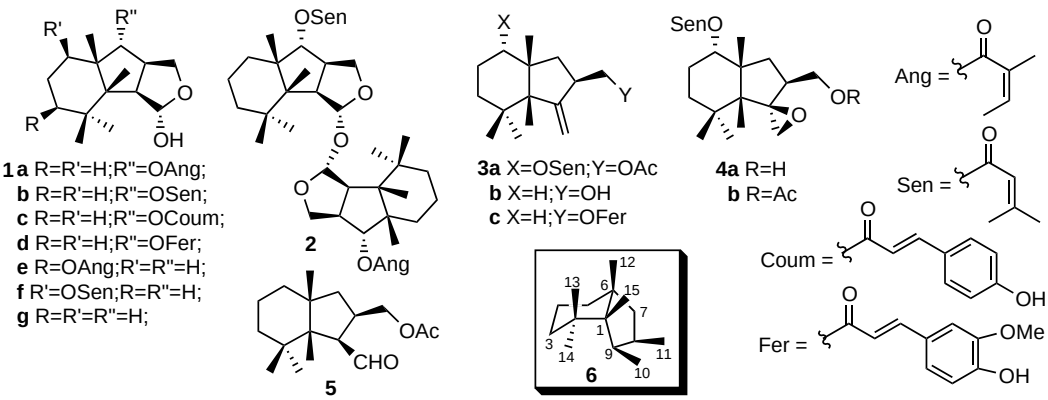
Abstract—Synthesis of (±)-3-methoxythapsene via stereospecific construction of three contiguous quaternary carbon atoms, employing a combination of a Claisen rearrangement and an intramolecular diazoketone cyclopropanation as key reactions, is described. © 2002 Published by Elsevier Science Ltd.

The presence of multiple quaternary carbon atoms is a common feature in a variety of natural products, particularly terpenoids. Even though several methods have been reported for the construction of a quaternary center, the presence of two or more quaternary carbon atoms in a contiguous manner provides challenging synthetic targets. In 1984, Rasmussen and co-workers reported[1] the isolation of the sesquiterpene **1a** from the ethanolic extract of the roots of the Mediterranean umbelliferous plant, *Thapsia villosa L.* Simultaneously, Grande and co-workers reported[2] the isolation of the corresponding senicioate ester **1b** from the benzene extract of the roots of *Thapsia villosa var minor*, along with five other hemiacetalic **1c**–**f**, **2**, and four non-



acetalic **3a**, **4a**,**b**, **5** minor components, having the same carbon framework. The trivial name 'thapsane' was suggested for the bicyclic carbon framework *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane (**6**) containing the three contiguous quaternary carbon atoms which are present in these sesquiterpenes. In 1990, Christensen and co-workers reported[3] the isolation of three more thapsanes, two nonacetalic **3b**,**c** and one hemiacetalic **1g**, from *T. villosa var minor*. The presence of an interesting carbon framework containing three contiguous quaternary carbon atoms make the thapsanes challenging synthetic targets. In continuation of our interest in the synthesis of racemic and optically active thapsanes,[4] we have developed an approach to thapsanes containing an oxygen functionality at the C-3 position starting from Hagemann's ester **7**, which is the subject of this communication.

Retrosynthetic analysis (Scheme 1) identified the bicyclic ketone **8**, which could be obtained from the tricyclic ketone **9**, as the ideal precursor for thapsanes containing an oxygen functionality at the C-3 position. It was contemplated that Claisen rearrangement of the allyl alcohol **10** followed by intramolecular cyclopropanation of the resultant γ,δ-unsaturated acid **11** could

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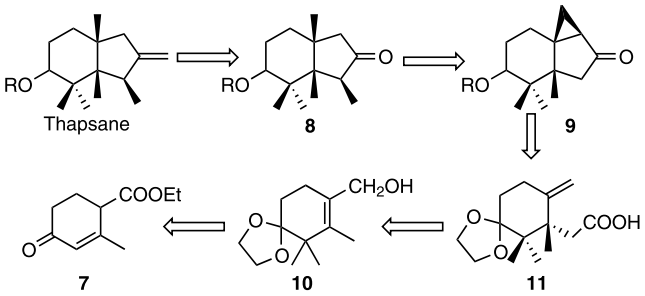
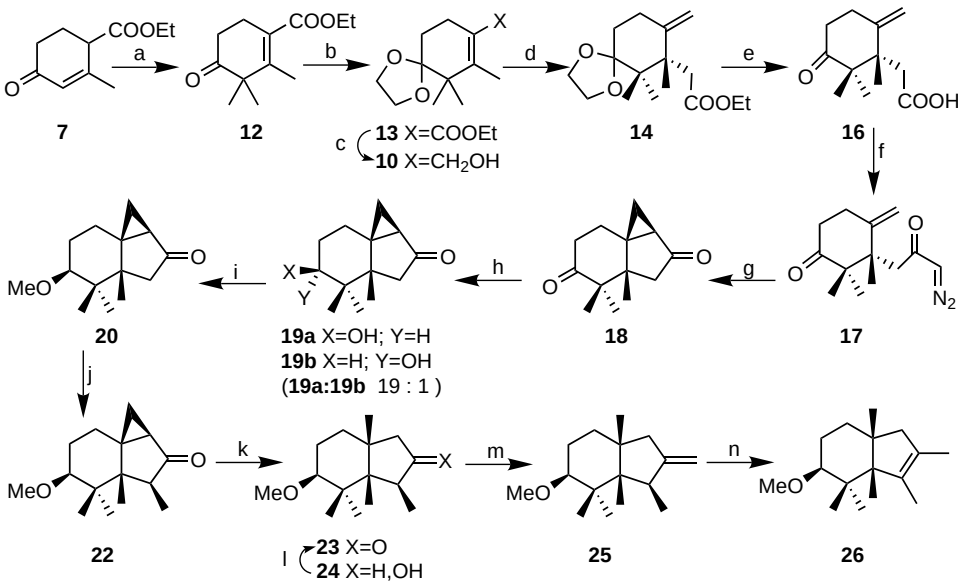


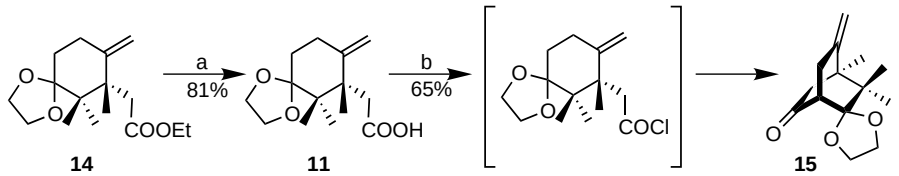
Scheme 1.

generate the tricyclic ketone **9**. Furthermore, Hagemann's ester **7** was considered as a suitable starting material for the preparation of the allyl alcohol **10**. Initially, the synthesis of the ketal-acid **11** was investigated (Schemes 2 and 3). Thus, dialkylation of the sodium dienolate of Hagemann's ester with methyl iodide at −100°C furnished regioselectively the γ,γ-dimethyl Hagemann's ester[5] **12** containing the first quaternary carbon atom. Ketalisation of the keto-ester **12** with ethanediol and *p*-toluenesulfonic acid (*p*-TSA) followed by regioselective reduction of the resultant ketal-ester **13** with lithium aluminum hydride (LAH) in ether at −70°C furnished the allyl alcohol **10**. Johnson's orthoester Claisen rearrangement[6] of the allyl alcohol **10** with triethyl orthoacetate and propionic acid in a sealed tube at 180°C created the second quaternary carbon atom to furnish the ketal-ester **14**, which on ester hydrolysis and careful acidification generated the ketal-acid **11** (Scheme 3).

For the creation of the third quaternary carbon atom, attention was focused on the conversion of the ketal-acid **11** into the corresponding diazoketone. However, reaction of the ketal-acid **11** with oxalyl chloride in benzene, both in the presence as well as in the absence



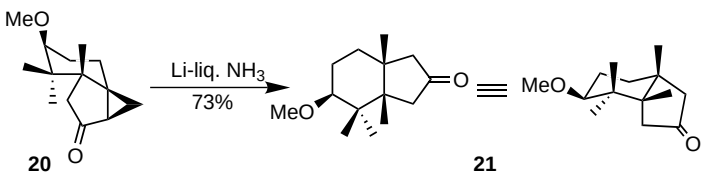
Scheme 2. *Reagents and conditions*: (a) i. NaH, THF, rt, 0.75 h, ii. MeI, −100°C, 1.5 h; rt, 7 h; 64%; (b) $(CH_2OH)_2$, *p*-TSA, C_6H_6, reflux (Dean–Stark), 5 h, 89%; (c) LAH, Et_2O, −70°C, 2 h, 90%; (d) $MeC(OEt)_3$, EtCOOH, sealed tube, 180°C, 7 days; 84%; (e) 5% NaOH in MeOH–H_2O (1:1), reflux, 7 h; 3N HCl, THF, 1 h; 97%; (f) i. $(COCl)_2$, C_6H_6, rt, 2 h, ii. CH_2N_2, Et_2O, rt, 2 h, 97%; (g) Cu, $CuSO_4$, *c*-C_6H_{12}, *W*-lamp, reflux, 5 h, 74%; (h) $NaBH_4$, MeOH, 0°C, 10 min, 100%; (i) NaH, THF, DMF, TBAI, MeI, 0°C–rt, 24 h, 94%; (j) LDA, THF, HMPA, MeI, 0°C–rt, 10 h, 87%; (k) Li, liquid NH_3, THF, 15 min, 81%; (l) PCC, CH_2Cl_2, rt, 3 h, 94%; (m) $Ph_3P^+CH_3I^-$, K^+ ^{t}AmO$^-$, C_6H_6, rt, 9 h, 84%; (n) *p*-TSA, CH_2Cl_2, rt, 6 h, 76%.



Scheme 3. (a) 5% NaOH in MeOH–H_2O (1:1), reflux, 7 h; (b) $(COCl)_2$, C_6H_6, DMF, rt, 1 h.

of triethylamine, furnished only the bicyclic ketoketal[†7] **15**, mp 61°C, in 65% yield, contrary to the expected acid chloride. To overcome this problem, the ketal moiety in **11** was hydrolysed to furnish the keto-acid **16**, which was converted into diazoketone **17** via the corresponding acid chloride. Stereospecific intramolecular cyclopropanation[8] of the diazoketone **17** with a mixture of copper powder and anhydrous copper sulphate in refluxing cyclohexane furnished the tricyclic dione **18**,[†] mp 198–200°C, in 74% yield. After accomplishing the synthesis of the tricyclic dione **18** containing three contiguous quaternary carbon atoms, differentiation of the two ketones in **18** was addressed and for this purpose the preferred reduction of cyclohexanones when compared to cyclopentanones was exploited.[9] Thus, regio- and stereoselective reduction of the dione **18** with one equivalent of sodium borohydride in methanol furnished a 19:1 mixture of the hydroxy-ketones **19a** and **19b** in quantitative yield, via preferred approach of the hydride from the less hindered equatorial side,[10] and which were separated by column chromatography on silica gel. Etherification of the hydroxy-ketone **19a** with sodium hydride and methyl iodide in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) in dimethylformamide (DMF) and THF furnished the methoxyketone[†] **20** in 94% yield, which on reaction with lithium in liquid ammonia[11] furnished the bicyclic ketone **21** (Scheme 4). The equatorial stereochemistry of the methoxy group in **21** was assigned on the basis of the coupling constants (11.0 and 3.3 Hz) of the axial proton attached to the methoxy bearing carbon, thus confirming the stereostructures of hydroxy-ketones **19a** and **19b**.

Next attention was turned towards the conversion of the methoxyketone **21** into thapsane, which requires the introduction of one carbon each at the C-8 and C-9 positions. To overcome the regiochemical problem, the methyl group was introduced prior to the cleavage of the cyclopropane ring. Thus, alkylation of the tricyclic ketone **20** with LDA and methyl iodide in THF and HMPA furnished the methylated ketone **22**, mp 80–82°C, in 87% yield, in a highly stereoselective manner,[12] which on regioselective cyclopropane ring cleavage[11] with lithium in liquid ammonia and THF furnished a 2:1 mixture of the bicyclic ketone **23**, mp 62°C, and the alcohol **24**, mp 93°C, in 81% yield, which were separated by column chromatography on silica gel. PCC oxidation transformed the alcohol **24** into the ketone **23**.[12] Finally, reaction of the ketone **23** with methylenetriphenylphosphorane in benzene at room temperature furnished 3-methoxythaps-8(11)-ene[†] **25** in 84% yield, which on isomerisation with a catalytic amount of

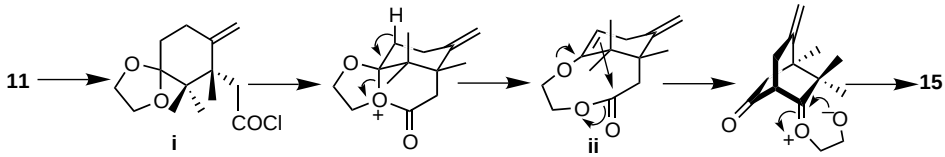


Scheme 4.

[†] All the compounds exhibited spectral data consistent with the structures. Selected spectral data for the ketoketal **15**: IR (thin film): ν_{max} 1728, 1646, 878 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.91 (1H, br s), 4.87 (1H, br s), 4.10–3.75 (4 H, m), 2.77 (1H, d, *J* 16.5 Hz), 2.55 (1H, d, *J* 19.0 Hz), 2.47 (1H, m), 2.43 (1H, m of d, *J* 16.5 Hz), 1.85 (1H, d, *J* 19.0 Hz), 1.05 (3H, s), 0.96 (3H, s), 0.94 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 210.1 (C), 148.1 (C), 110.8 (C), 108.0 (CH_2), 64.9 (CH_2), 64.4 (CH_2), 54.2 (CH), 46.9 (CH_2), 45.0 (C), 43.5 (C), 28.4 (CH_2), 21.6 (CH_3), 19.9 (CH_3), 17.2 (CH_3). For the dione **18**: mp: 198–200°C. IR (thin film): ν_{max} 1728, 1706 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88 (1H, dt, *J* 14.0 and 7.5 Hz), 2.47 (1H, dt, *J* 14.4 and 5.7 Hz), 2.26 (1H, ddd, *J* 13.5, 5.7 and 2.0 Hz), 2.11 (1H, d, *J* 18.0 Hz), 2.08 (1H, dd, *J* 7.8 and 2.4 Hz), 1.87 (1H, dd, *J* 18.0 and 1.0 Hz), 1.62 (1H, ddd, *J* 13.5, 7.8 and 1.5 Hz), 1.19 (3H, s), 1.09 (1H, dd, *J* 5.1 and 3.0 Hz), 1.07 (3H, s), 0.98 (3H, s), 1.00–0.90 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.0 (C), 211.2 (C), 51.8 (C), 46.9 (C), 43.0 (CH_2), 37.0 (CH), 35.5 (2 C, C and CH_2), 28.5 (CH_2), 23.2 (CH_3), 20.1 (CH_3), 19.0 (CH_3), 16.7 (CH_2). For the methoxyketone **20**: IR (neat): ν_{max} 1726 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.30 (3H, s), 2.94 (1H, br s), 2.31 (1H, dt, *J* 14.0 and 5.1 Hz), 2.02 (1H, d, *J* 18.0 Hz), 1.90–1.70 (4 H, m), 1.64 (1H, d, *J* 18.0 Hz), 1.27 (3H, s), 1.04 (1H, dd, *J* 5.0 and 2.7 Hz), 0.96 (3H, s), 0.87 (3H, s), 0.95–0.75 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.7 (C), 86.8 (CH), 57.5 (CH_3), 45.4 (CH_2), 42.7 (C), 40.8 (C), 37.0 (C), 36.97 (CH), 24.9 (CH_3), 22.9 (CH_2), 22.5 (CH_3), 21.6 (CH_2), 21.2 (CH_3), 17.7 (CH_2). For the tricyclic ketone **22**: IR (thin film): ν_{max} 1723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.31 (3H, s), 2.96 (1H, br s), 2.32 (1H, dt, *J* 14.0 and 5.7 Hz), 2.12 (1H, q, *J* 8.0 Hz), 1.84 (1H, br d, *J* 9 Hz), 1.85–1.65 (3H, m), 1.21 (3H, s), 1.02 (3H, d, *J* 8.0 Hz), 0.92 (3H, s), 0.90–0.80 (1H, m), 0.85 (3H, s), 0.74 (1H, dd, *J* 9.0 and 5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 216.9 (C), 87.2 (CH), 57.6 (CH_3), 47.3 (CH), 44.5 (C), 41.9 (C), 37.1 (C), 36.9 (CH), 24.8 (CH_3), 23.4 (CH_2), 22.3 (CH_3), 21.5 (CH_2), 17.4 (CH_2), 17.3 (CH_3), 16.5 (CH_3). For the bicyclic ketone **23**: IR (thin film): ν_{max} 1737 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.34 (3H, s), 3.05 (1H, m of d, *J* 8 Hz), 2.56 (1H, q, *J* 7.2 Hz), 2.22 (1H, d, *J* 18.3 Hz), 1.90 (1H, dd, *J* 18.3 and 1.5 Hz), 1.85–1.75 (1H, m), 1.55–1.40 (3H, m), 1.22 (3H, s), 1.10 (3H, d, *J* 7.2 Hz), 0.98 (3H, s), 0.94 (3H, s), 0.91 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 219.8 (C), 84.4 (CH), 57.6 (CH_3), 53.4 (CH_2), 49.7 (C), 49.0 (CH), 41.8 (C), 39.8 (C), 35.6 (CH_2), 24.9 (CH_3), 23.0 (CH_3), 22.6 (CH_2), 18.0 (CH_3), 13.8 (CH_3), 13.4 (CH_3). For 3-methoxythaps-8(11)-ene **25**: IR (neat): ν_{max} 1650, 880 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.82 (1H, m), 4.77 (1H, m), 3.33 (3H, s), 3.04 (1H, dd, *J* 11.4 and 4.0 Hz), 2.82–2.70 (1H, m), 2.38 (1H, qd, *J* 16.0 and 2.7 Hz), 1.84 (1H, d, *J* 16.0 Hz), 1.80–1.60 (1H, m), 1.60–1.15 (3H, m), 1.08 (3H, d, *J* 6.6 Hz), 1.06 (3H, s), 0.96 (3H, s), 0.86 (3H, s), 0.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.3 (C), 106.3 (CH_2), 84.8 (CH), 57.6 (CH_3), 51.0 (C), 49.1 (CH_2), 42.6 (C), 42.58 (CH), 41.7 (C), 34.6 (CH_2), 24.7 (CH_3), 23.1 (CH_3), 22.8 (CH_2), 18.4 (CH_3), 17.7 (CH_3), 13.4 (CH_3). For 3-methoxythaps-8-ene **26**: ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.25 (3H, s), 2.81 (1H, dd, *J* 6.0 and 3.0 Hz), 2.18 (1H, d, *J* 15.3 Hz), 1.70–1.50 (3H, m), 1.55 (3H, s), 1.54 (3H, s), 1.40–1.20 (2 H, m), 0.94 (3H, s), 0.90 (3H, s), 0.86 (3H, s), 0.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 137.2 (C), 129.8 (C), 86.5 (CH), 57.0 (CH_3), 55.6 (C), 51.4 (CH_2), 43.2 (C), 41.8 (C), 30.0 (CH_2), 29.0 (CH_3), 26.6 (CH_3), 24.5 (CH_3), 20.9 (CH_2), 17.1 (CH_3), 14.5 (CH_3), 13.6 (CH_3).

p-TSA furnished 3-methoxythaps-8-ene† **26** in 76% yield. Synthesis of **25** and **26** constitutes the first total synthesis of thapsenes containing an oxygen functionality at the C-3 position.

In conclusion, we have accomplished the synthesis of (±)-3-methoxythaps-8-ene. A Claisen rearrangement and an intramolecular cyclopropanation reaction were employed for the stereospecific construction of the three contiguous quaternary carbon atoms.



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References

1. Lemmich, E.; Jensen, B.; Rasmussen, U. *Phytochemistry* **1984**, *23*, 809.
2. (a) Teresa, J. P.; Moran, J. R.; Grande, M. *Chem. Lett.* **1985**, 865; (b) Teresa, J. P.; Moran, J. R.; Fernandez, A.; Grande, M. *Phytochemistry* **1986**, *25*, 703; (c) Teresa, J. P.; Moran, J. R.; Fernandez, A.; Grande, M. *Phytochemistry* **1986**, *25*, 1171.
3. Smitt, U. W.; Cornett, C.; Norup, E.; Christensen, S. B. *Phytochemistry* **1990**, *29*, 873.
4. For synthesis of racemic thapsanes, see: (a) Srikrishna, A.; Krishnan, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 667; (b) Srikrishna, A.; Krishnan, K. *J. Org. Chem.* **1993**, *58*, 7751. For enantiospecific synthesis of (−)-thaps-8-en-5-ol, see: (c) Srikrishna, A.; Anebouselvy, K.; Reddy, T. J. *Tetrahedron Lett.* **2000**, *41*, 6643; (d) for (+)-thaps-8(11)-en-3-ol, see the accompanying paper: Srikrishna, A.; Anebouselvy, K. *Tetrahedron Lett.* **2002**, *43*, 2769.
5. White, J. D.; Sung, W. L. *J. Org. Chem.* **1974**, *39*, 2323.
6. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
7. Formation of the ketoketal **15** from the acid **11** can be explained via the acid chloride **i** as depicted below. Intramolecular *O*-acylation of the ketal oxygen followed by elimination of a proton transforms the acid chloride **i** into the enol-lactone **ii**, which undergoes cyclisation and bond reorganization to generate the ketoketal **15**.
8. (a) Stork, G.; Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678; (b) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361; (c) Mander, L. N. *Synlett* **1991**, 134; (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.
9. Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206.
10. Chang, C.-W. T.; Hui, Y.; Elchert, B. *Tetrahedron Lett.* **2001**, *42*, 7019.
11. (a) Norin, T. *Acta Chem. Scand.* **1963**, *17*, 738; (b) Norin, T. *Acta Chem. Scand.* **1965**, *19*, 1289; (c) Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 2361; (d) Srikrishna, A.; Krishnan, K.; Yelamaggad, C. V. *Tetrahedron* **1992**, *48*, 9725.
12. The stereochemistry of the methoxy and secondary methyl groups in **22** was confirmed by X-ray crystal structure, whereas stereochemistry of the secondary methyl group in **23** was assigned on the basis of thermodynamic considerations. The methyl group in **23** did not isomerise under equilibrating conditions indicating the thermodynamic nature. Molecular mechanics calculations indicated that the *exo* isomer **23** is 4.90 kcal/mol more stable than the corresponding *endo* isomer.