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Tetrahedron Letters 44 (2003) 1031–1034

TETRAHEDRON LETTERS

Enantiospecific first total synthesis of (+)-*cis*,*anti*,*cis*-3-hydroxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]-dodecan-9-yl senecioate, the optical antipode of a natural thapsane isolated from *Thapsia villosa*☆

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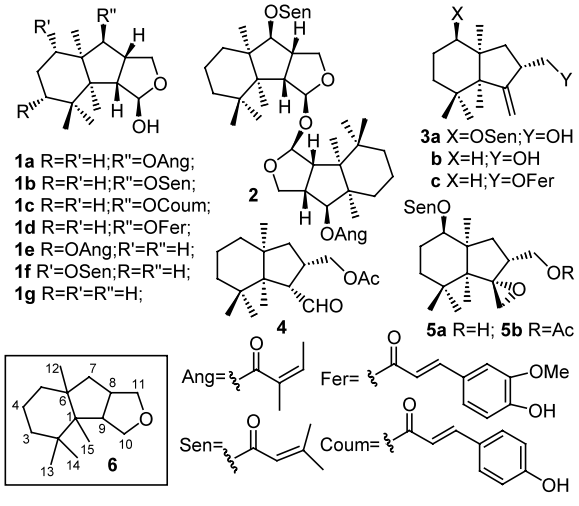
Received 1 October 2002; revised 21 November 2002; accepted 29 November 2002

Abstract—The enantiospecific first total synthesis of 10-hydroxy-10,11-epoxythapsan-5-yl senecioate (+)-**1f**, the enantiomer of the natural thapsane isolated from *Thapsia villosa* var *minor*, has been accomplished starting from (*R*)-carvone.

The medicinal properties of plants belonging to the Mediterranean umbelliferous genus *Thapsia* were recognised as early as 300 BC.[1] Interest in the genus *Thapsia* arose when the two guaianolides, thapsigargin and thapsigargicin (the active principles present in *Thapsia garganica*) were recognised as highly potent histamine liberators, general stimulants of the immune system, non-TPA tumour promoters and selective inhibitors of the microsomal Ca^{2+}-ATPases. Phytochemical investigations on *Thapsia villosa* led to the isolation of a new group of sesquiterpenes, thapsanes, which are unique to the species. The research groups of Rasmussen,[2] Grande[3] and Christensen[4] reported the isolation of eight hemiacetalic **1a**–**g**, **2**, and six nonacetalic **3a**–**c**, **4**, **5a**,**b** thapsanes, having novel carbon frameworks from the extract of the roots of *T. villosa* var *minor*. The structures of the thapsanes were assigned on the basis of spectral data and were supported by the X-ray crystal structure of **1a**. Rasmussen et al. assigned the absolute configuration of the thapsane **1a** employing the empirical method of Horeau, which is opposite to that assigned[5] to all thapsanes by Grande et al., on the basis of the CD-curves of the ketones derived from the thapsanes **1e**,**f**. A characteristic of the structure of the hemiacetalic thapsanes is the presence of a *cis*,*anti*,*cis*-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecane framework **6** (10,11-epoxythapsane), containing three contiguous quaternary carbon atoms and five to six chiral centres, which poses a significant synthetic challenge. So far, among the natural thapsanes, synthesis of only the simplest member, **1g**, has been reported.[6] Herein, we report the first enantiospecific total synthesis of the optical antipode of the thapsane **1f**, which has an ester group at the C-5 carbon, starting from the readily and abundantly available monoterpene, (*R*)-carvone (**7**).



For the enantiospecific synthesis of the thapsane **1f**, we conceived a combination of our earlier approach to racemic thapsane[6a] **1g** and the recently developed[7]

☆ Chiral synthons from carvone, Part 58. For parts 56 and 57, see Ref. 12.

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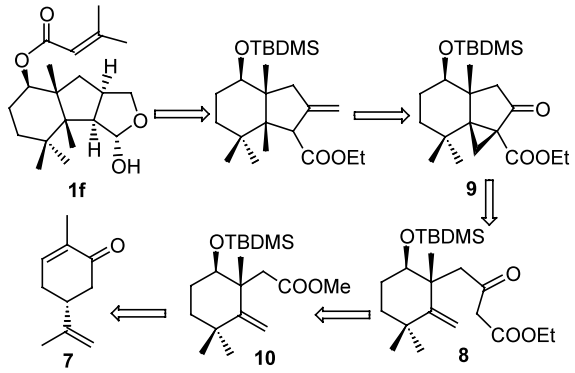
PII: S0040-4039(02)02733-8

enantiospecific synthesis of a thapsenol. It was anticipated that intramolecular cyclopropanation of the diazoketone derived from the β-ketoester **8** would generate the tricyclic ketone **9**, which could be further elaborated into thapsane **1f**. It was contemplated that the ester **10**, which could be obtained from (*R*)-carvone (**7**) in optically active form,[7] would serve as an ideal precursor for the generation of the β-ketoester **8** (Scheme 1).

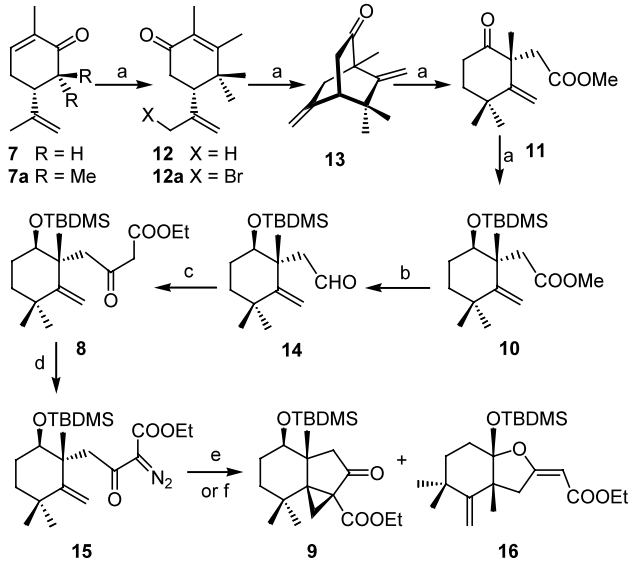
The synthetic sequence starting from (*R*)-carvone (**7**) is depicted in Schemes 2 and 3. To begin with, as



Scheme 1.

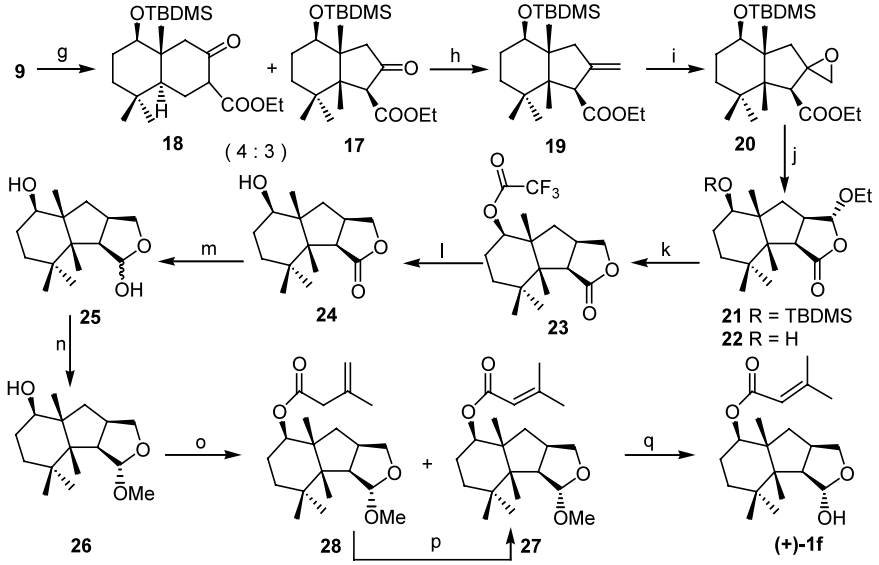
described earlier,[7] (*R*)-carvone (**7**) was converted into the ketoester **11**, via trimethylcarvone **12** and bicyclo[2.2.2]octanone **13**, employing a regio-, stereo- and enantiospecific translocation of the isopropenyl side chain of trimethylcarvone from the C-5 carbon to the C-2 carbon (as an acetate side chain) strategy. The keto-ester **11** was transformed into the silyloxy ester **10** employing an intramolecular hydride reduction of the ketone as the key step.[7] The ester **10** was transformed into the β-ketoester **8** via the aldehyde **14**. Thus, lithium aluminium hydride (LAH) reduction of the ester **10** followed by PCC oxidation of the resultant alcohol generated the aldehyde **14**, $[\alpha]_D^{24}$ −8.5 (*c* 4, $CHCl_3$). Stannous chloride catalysed coupling[8] of the aldehyde **14** with ethyl diazoacetate furnished the β-ketoester **8**, $[\alpha]_D^{26}$ −34 (*c* 1, $CHCl_3$), in 92% yield. Diazo transfer reaction with tosyl azide and triethylamine converted the ketoester **8** into the α-diazo-β-ketoester **15** in 90% yield. A rhodium acetate catalysed stereospecific intramolecular cyclopropanation[9] reaction of the diazo compound **15** resulted in the formation of the tricyclic compound† **9**, in 45% yield, along with 9% of the unexpected byproduct† **16**. The formation of the byproduct **16** can be rationalised via C–H insertion of the intermediate rhodium carbenoid through the oxygen of the ketone.[10] On the other hand, treatment of

† All compounds exhibited spectral data consistent with their structures. Yields refer to isolated and chromatographically pure compounds. Spectral data for the tricyclic compound **9**: $[\alpha]_D^{25}$: −27.86 (*c* 1.4, $CHCl_3$). IR (neat): ν_{max} 1742, 1722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.17 (2H, q, J=7.0 Hz), 3.35 (1H, dd, J=11.1 and 4.2 Hz), 2.22 and 1.83 (2H, 2×d, J=18.0 Hz), 1.85–1.50 (4H, m), 1.46 (1H, t of d, J=13.5 and 3.6 Hz), 1.33–1.26 (1H, m), 1.28 (3H, t, J=7.0 Hz), 1.13 (3H, s), 1.11 (3H, s), 0.60 (3H, s), 0.85 (9H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 207.0 (C), 167.9 (C), 76.5 (CH), 61.2 (CH_2), 53.5 (C), 49.0 (C), 45.3 (CH_2), 44.8 (C), 37.0 (CH_2), 33.0 (C), 28.2 (CH_3), 27.5 (CH_2), 27.0 (CH_3), 25.8 (3C, CH_3), 18.05 (CH_3), 18.0 (C), 17.6 (CH_2), 14.0 (CH_3), −3.7 (CH_3), −5.0 (CH_3). For the compound **16**: $[\alpha]_D^{25}$: +31.7 (*c* 1.2, $CHCl_3$). IR (neat): ν_{max} 1718, 1700, 1663, 891 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.06 (1H, s), 5.00 (1H, s), 4.72 (1H, d, J=1.1 Hz, C=CH), 4.14 and 4.06 (2H, q of AB q, J=10.6 and 7.0 Hz, OCH_2CH_3), 2.95 (1H, d, J=16.2 Hz), 2.76 (1H, dd, J=16.2 Hz and 1.6 Hz), 2.15 (1H, t of d, J=14.3 and 4.0 Hz), 1.98 (1H, d of t, J=14.0 and 4.0 Hz), 1.63 (1H, d of t, J=13.2 and 4.0 Hz), 1.36 (1H, t of d, J=14.0 and 4.0 Hz), 1.24 (3H, t, J=7.0 Hz), 1.30 (3H, s), 1.15 (3H, s), 1.11 (3H, s), 0.88 (9H, s), 0.25 (3H, s), 0.10 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 168.8 (C), 165.2 (C), 157.8 (C), 112.6 (C), 110.1 (CH_2), 89.2 (CH, O-C=*C*H), 58.9 (CH_2), 50.2 (C), 45.9 (CH_2), 35.4 (C), 35.2 (CH_2), 31.3 (CH_3), 30.1 (2 C, CH_3 and CH_2), 25.9 (3C, CH_3), 25.5 (CH_3), 18.1 (C), 14.6 (CH_3), −2.9 (CH_3), −3.8 (CH_3). For the compound **19**: $[\alpha]_D^{24}$: +20.5 (*c* 4.0, $CHCl_3$). IR (neat): ν_{max} 1745, 1717, 1653, 883 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.91 (1H, s), 4.83 (1H, s), 4.22–4.02 (2H, m), 3.63 (1H, br s), 3.41 (1H, dd, J=10.5 and 4.2 Hz), 2.44 and 2.28 (2H, 2×d, J=16.2 Hz), 1.75–1.35 (4H, m), 1.27 (3H, t, J=6.9 Hz), 1.12 (3H, s), 1.00 (3H, s), 0.98 (3H, s), 0.81 (3H, s), 0.88 (9H, s), 0.02 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 173.4 (C), 148.9 (C), 108.5 (CH_2), 72.9 (CH), 59.9 (CH_2), 54.7 (CH), 54.3 (C), 49.9 (C), 44.0 (CH_2), 36.7 (CH_2), 36.2 (C), 28.6 (CH_3), 27.9 (CH_2), 26.1 (3C, CH_3), 25.3 (CH_3), 18.2 (C), 15.5 (CH_3), 14.9 (CH_3), 14.5 (CH_3), −3.6 (CH_3), −4.7 (CH_3). For the ethoxy lactone **21**: $[\alpha]_D^{25}$: −40.0 (*c* 0.6, $CHCl_3$). IR (neat): ν_{max} 1772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.14 (1H, s), 3.87 (1H, q of d, J=9.3 and 6.9 Hz), 3.56 (1H, q of d, J=9.3 and 6.9 Hz), 3.39 (1H, dd, J=10.8 and 3.6 Hz), 3.30 (1H, d, J=11.1 Hz), 2.75 (1H, q, J=9.9 Hz), 2.23 (1H, dd, J=12.9 and 9.3 Hz), 1.70–1.20 (5H, m), 1.23 (3H, t, J=6.9 Hz), 1.07 (3H, s), 1.01 (3H, s), 0.97 (3H, s), 0.94 (3H, s), 0.89 (9H, s), 0.06 (3H, s), 0.055 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6 (C), 107.9 (CH), 73.0 (CH), 64.9 (CH_2), 53.8 (C), 53.3 (C), 51.6 (CH), 44.2 (CH), 40.3 (CH_2), 36.9 (CH_2), 35.7 (C), 30.3 (CH_3), 27.6 (CH_2), 25.8 (3C, CH_3), 24.5 (CH_3), 18.0 (C), 15.8 (CH_3), 15.3 (CH_3), 14.9 (CH_3), −3.7 (CH_3), −4.9 (CH_3). For the trifluoroacetate **23**: mp 100–102°C. $[\alpha]_D^{23}$: +34.28 (*c* 1.4, $CHCl_3$). IR (neat): ν_{max} 1776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.99 (1H, dd, J=12.2 and 4.4 Hz), 4.44 (1H, t, J=9.2 Hz), 3.96 (1H, dd, J=9.6 and 3.9 Hz), 3.30–3.10 (2H, m), 2.00–1.40 (6H, m), 1.17 (3H, s), 1.15 (3H, s), 1.05 (3H, s), 1.04 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8 (C), 157.5 (C, q, $^2J_{C-F}$=42 Hz), 114.5 (C, q, $^1J_{C-F}$=284 Hz), 80.3 (CH), 72.7 (CH_2), 54.4 (C), 52.6 (C), 50.7 (CH, C-2), 43.8 (CH_2), 36.3 (CH_2), 35.9 (C), 35.6 (CH), 30.2 (CH_3), 24.5 (CH_3), 23.6 (CH_2), 16.0 (CH_3), 15.1 (CH_3). For the (+)-hydroxyacetal **26**: mp 110–112°C (lit.:[3b] 112–114°C). $[\alpha]_D^{24}$: +64.3 (*c* 0.7, $CHCl_3$) [lit.[3b] for (−)-**26**: −67.5 (*c* 2.4, $CHCl_3$)]. IR (thin film): ν_{max} 3479 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.79 (1H, s), 3.96 (1H, t, J=7.8 Hz), 3.63 (1H, d, J=7.8 Hz), 3.64–3.58 (1H, m), 3.27 (3H, s), 2.85–2.74 (2H, m), 2.25–2.10 (1H, m), 1.80–1.50 (4H, m), 1.35–1.20 (2H, m), 0.96 (6H, s), 0.88 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.3 (CH), 72.5 (CH_2), 72.4 (CH), 57.7 (CH), 54.3 (CH_3), 53.4 (C), 50.1 (C), 43.4 (CH_2), 38.0 (CH), 36.5 (CH_2), 35.8 (C), 28.0 (CH_3), 27.6 (CH_2), 24.6 (CH_3), 14.7 (CH_3), 13.4 (CH_3). For the thapsane **1f**: $[\alpha]_D^{23}$: +37.3 (*c* 1.1, $CHCl_3$) [lit.[3b] for (−)-**1f**: −35.7 (*c* 4.7, $CHCl_3$)]. IR (neat): ν_{max} 3408, 1714, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.67 (1H, s), 5.36 (1H, s), 4.99 (1H, dd, J=11.4 and 4.5 Hz), 4.14 (1H, t, J=8.0 Hz), 3.62 (1H, d, J=8.0 Hz), 3.05–2.85 (2H, m), 2.21 (1H, br s), 2.17 (3H, s), 1.89 (3H, s), 1.95–1.50 (4H, m) 1.35–1.20 (2H, m), 1.05 (3H, s), 0.99 (3H, s), 0.94 (3H, s), 0.89 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (C), 156.3 (C), 116.4 (CH), 100.7 (CH), 73.5 (CH), 72.8 (CH_2), 58.3 (CH), 52.3 (C), 50.6 (C), 43.5 (CH_2), 38.0 (CH), 36.2 (CH_2), 35.8 (C), 28.1 (CH_3), 27.4 (CH_3), 24.6 (CH_3), 24.3 (CH_2), 20.2 (CH_3), 16.0 (CH_3), 13.2 (CH_3).



Scheme 2. *Reagents, conditions and yields*: (a) Ref. 7; (b) i. LAH, Et_2O, 0°C–rt, 2 h, 91%; ii, PCC, silica gel, CH_2Cl_2, rt, 3 h, 90%; (c) N_2CHCO_2Et, $SnCl_2{\cdot}2H_2O$, CH_2Cl_2, rt, 6 h, 92%; (d) *p*-TsN_3, NEt_3, CH_3CN, rt, 12 h, 90%; (e) $Rh_2(OAc)_4$, C_6H_6, rt, 20 h, 45% of **9** and 9% of **16**; (f) Cu, $CuSO_4$, *c*-C_6H_{12}, *W*-lamp, 24 h, 60% of **9**.

the α-diazo-β-ketoester **15** with copper and anhydrous copper sulfate in refluxing cyclohexane in the presence of a tungsten lamp furnished, exclusively, the tricyclic β-keto ester **9**, in 60% yield. Reductive cleavage of the cyclopropane ring in **9** employing lithium in liquid ammonia furnished a 3:4 mixture of the hydrindanone **17**, mp 85–87°C, $[\alpha]_D^{22}$ +67.5 (*c* 1.2, $CHCl_3$), and the decalinone **18**, $[\alpha]_D^{22}$ −38 (*c* 1.3, $CHCl_3$), in 78% yield, via electron transfer to the ketone and ester carbonyl groups,[11] respectively. Wittig reaction of the ketoester **17** with methyltriphenylphosphonium bromide and potassium *tert*-amylate in refluxing benzene generated the ester† **19** in quantitative yield. Epoxidation of the exomethylene in **19** with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride generated a ≈2:1 epimeric mixture of the epoxides **20** in 80% yield. Treatment of the epimeric mixture of the epoxides **20** with a catalytic amount of boron trifluoride diethyl etherate in methylene chloride furnished a ≈1:1 mixture of the ethoxylactone† **21** and the desilylated lactone **22**, $[\alpha]_D^{23}$ −59.4 (*c* 1.6, $CHCl_3$), in 70% yield, which were separated by silica gel column chromatography. Formation of the ethoxylactones **21** and **22** can be rationalised via the boron trifluoride diethyl etherate-catalysed rearrangement of the epoxide in **20** followed by intramolecular transacetalisation of the resultant ester aldehyde. Ionic hydrogenation of either of the ethoxylactones **21** or **22** using a combination of trifluoroacetic acid and triethylsilane furnished the trifluoroacetoxy lactone# **23**, which on hydrolysis with potassium carbonate in methanol furnished the hydroxylactone **24**, $[\alpha]_D^{23}$ +40 (*c* 0.9, $CHCl_3$), mp 177–179°C (lit.[3b] 184–186°C), a degradation product of the thapsane **1f**, which exhibited IR and ^1H NMR spectra identical to those of the authentic sample.[3] Controlled reduction of the lactone moiety in **24** with diisobutylaluminum hydride (DIBAL-H) furnished an epimeric mixture of the hydroxy hemiacetal **25**, which on acetalisation with methanol in the presence of PTSA furnished the hydroxyacetal† **26**. Coupling of the hydroxyacetal **26** with senecioic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) generated a mixture of the senecioate **27** and the deconjugated ester **28**, which was quantitatively equilibrated



Scheme 3. *Reagents, conditions and yields*: (g) Li, liq. NH_3, THF, −33°C, 10 min, 78%; (h) $Ph_3P^+CH_3\ Br^-$, $K^{+t}AmO^-$, C_6H_6, reflux, 12 h, 99%; (i) MCPBA, CH_2Cl_2, rt, 24 h, 80%; (j) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 0.5 h, 70%; (k) Et_3SiH, CF_3COOH, reflux, 4–5 h, 70%; (l) K_2CO_3, MeOH, rt, 6 h, 95%; (m) DIBAL-H, PhMe, −78°C, 1 h, 89%; (n) MeOH, *p*-TSA, 10 min, rt, 84%; (o) $Me_2C{=}CHCOOH$, DCC, DMAP, PhMe, rt, 24 h, 99%; (p) DBU, CH_2Cl_2, rt, 9 h, 100%; (q) 3N HCl, THF, rt, 0.8 h, 96%.

to **27**, $[\alpha]_D^{24}$ +48.5 (*c* 1.3, $CHCl_3$), with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride. Finally, hydrolysis of the acetal moiety in **27** furnished the thapsane[†] **1f**. The thapsane **1f** exhibited IR, ^1H NMR and mass spectra identical to those of the natural product, but the opposite optical rotation.[3b,5]

In conclusion, we have accomplished the first enantiospecific total synthesis of the optical antipode of the hemiacetalic thapsane **1f** containing a senecioate moiety at the C-5 position. Currently, we are investigating the extension of this methodology to other natural thapsanes.

Acknowledgements

We thank Professor M. Grande, Universidad de Salamanca, for providing the copies of the spectra of the compounds **24**, **27** and **1f**. We are grateful to D.S.T. for financial support, and the C.S.I.R. for the award of a research fellowship to KAS.

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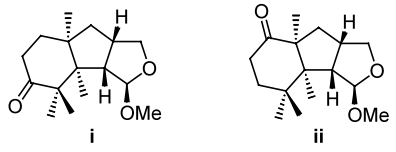

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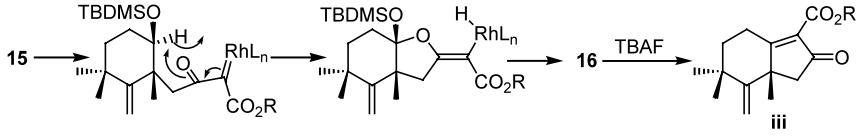

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