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An enantiospecific approach to thapsanes from *R*-carvone: synthesis of (–)-thaps-8-en-5-ol†

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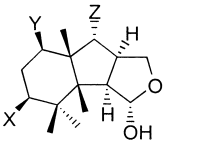
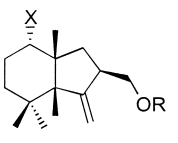
Abstract

The first enantiospecific synthesis of a thapsane, containing three contiguous quaternary carbon atoms, is accomplished starting from *R*-carvone. An intramolecular alkylation and an intramolecular diazoketone cyclopropanation reaction were employed for the stereo- and regiospecific generation of three contiguous quaternary carbon atoms present in the thapsane framework. © 2000 Published by Elsevier Science Ltd.

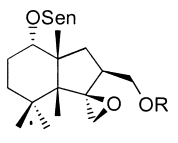
Thapsanes **1–4** are a small group of sesquiterpenes isolated from the Mediterranean umbelliferous plant *Thapsia villosa*.[1] A characteristic of the structure of the thapsanes is the presence of a *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane carbon framework **5** incorporating three contiguous quaternary carbon atoms, posing a significant synthetic challenge. Even though the synthesis of the thapsane carbon framework and subsequently one of the natural thapsanes **1g** in racemic form were achieved,[2] there is no report on the synthesis of thapsanes in optically active form. Herein we report an enantiospecific approach to the thapsane carbon framework containing an oxygen functionality at the C-5 carbon, starting from *R*-carvone **6**.



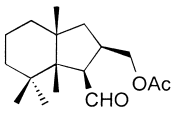
1a: X=Y=H; Z=OAng
b: X=Y=H; Z=OSen
c: X=Y=H; Z=OCoum
d: X=Y=H; Z=OFer
e: X=Z=H; Y=OSen
f: Y=Z=H; X=OAng
g: X=Y=Z=H



2a: X=OSen; R=H
b: X=R=H
c: X=H; R=Fer



3a: R=H
b: R=Ac



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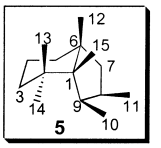

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Retrosynthetic analysis on the basis of an intramolecular diazoketone cyclopropanation reaction is depicted in Scheme 1. It was anticipated that intramolecular cyclopropanation of the

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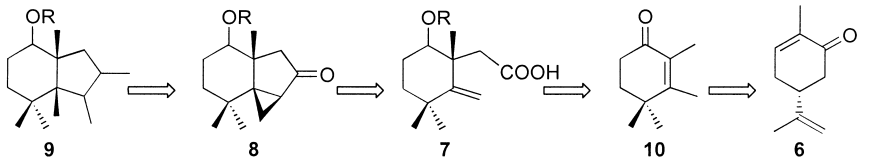
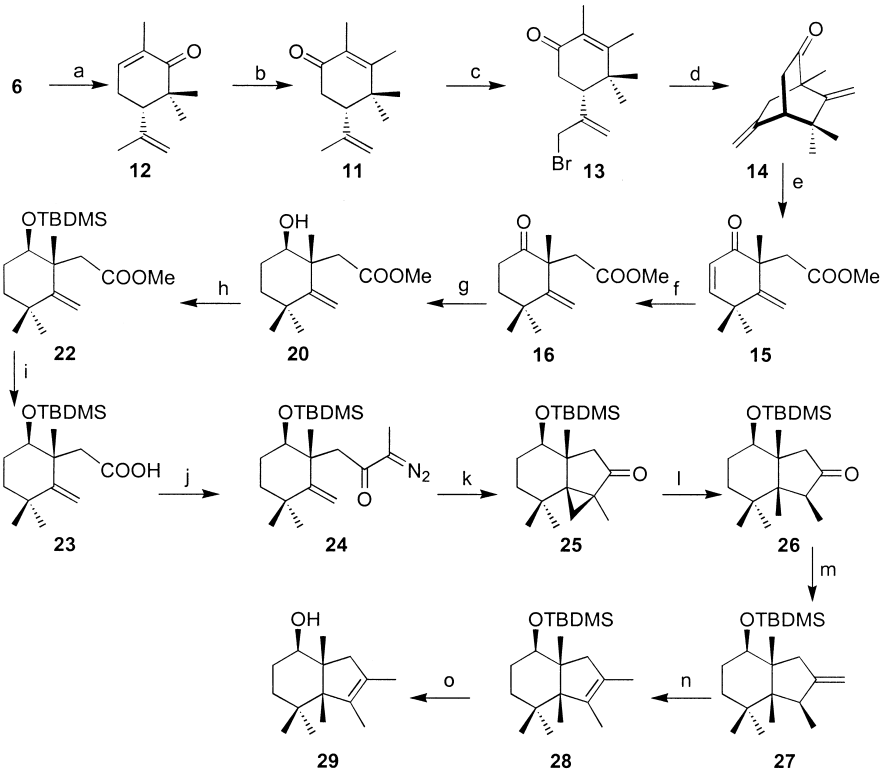
diazoketone derived from the acid **7** would generate the tricyclic ketone **8**, which can be further elaborated to thapsane **9**. Alkylation at the α-position of the enone with an equivalent of CH_2COOH suggested the enone **10** as the appropriate precursor for the acid **7**. Identifying the isopropenyl group as a masked hydroxy group, *R*-carvone **6** was chosen as the chiral precursor for the generation of a chiral analogue of the enone **10**. The synthetic sequence starting from *R*-carvone **6** is depicted in Scheme 2. To begin with, *R*-carvone **6** was transformed into *R*-3,4,4-trimethylcarvone **11**. Sequential kinetic alkylation of carvone **6** with LDA and methyl iodide furnished the 6,6-dimethylcarvone **12**,[3] which was transformed into the enone **11** via an alkylative enone transposition strategy.



Scheme 1.



Scheme 2. Reagents and conditions: (a) Ref. 3; (b) i. MeMgI, Et_2O, 0°C to rt, 12 h; ii. PCC, silica gel, CH_2Cl_2, rt, 6 h, 60%; (c) NBS, CH_2Cl_2:MeOH (3:2), 0°C to rt, 6 h, 90%; (d) ^{t}BuOK, ^{t}BuOH–THF, –5°C to rt, 12 h, 70%; (e) i. O_3/O_2, MeOH:CH_2Cl_2 (1:4), $NaHCO_3$, –70°C; ii. Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 6 h; 67% (60% conversion); (f) 5% Pd/C, H_2, EtOAc, 30 min, 90%; (g) Scheme 3; (h) TBDMSCl, DMAP, DMF, rt, 48 h, 95%; (i) 5% NaOH in MeOH:H_2O (1:1), reflux, 12 h, 95%; (j) i. $(COCl)_2$, py, C_6H_6, rt, 3 h; ii. CH_3CHN_2, Et_2O, 0°C, 2 h; (k) Cu–$CuSO_4$, *c*-C_6H_{12}, W-lamp, reflux, 5 h, 47% (from the acid **23**); (l) Li, liq. NH_3, ^{t}BuOH, –33°C, 2 h, 82% (85% conversion); (m) ^{t}BuOK, Ph_3PCH_3Br, C_6H_6, 70°C, 4 h, 75% (82% conversion); (n) p-TSA, CH_2Cl_2, rt, 6 h, 62%; (o) TBAF, THF, reflux, 24 h, 90%

Reaction of the enone **12** with methylmagnesium iodide followed by oxidation of the resulting allyllic tertiary alcohol with pyridinium chlorochromate and silica gel furnished the enone **11**. Instead of the degradation of the isopropenyl group and introduction of an acetic acid side chain at the C-2 position, translocation of the isopropenyl group from C-5 to the C-2 position as the acetic acid side chain was envisaged. An intramolecular alkylation methodology was adopted for joining the C-2 carbon of the enone **11** with the isopropenyl group.[4] Thus, reaction of trimethylcarvone **11** with *N*-bromosuccinimide (NBS) in a methanol–methylene chloride medium furnished the allyl bromide **13** in 90% yield.[5] Treatment of the allyl bromide **13** with potassium *tert*-butoxide in *tert*-butanol–THF furnished the bicyclo[2.2.2]octanone **14**‡ via regioselective intramolecular alkylation of the intermediate dienolate. The steric hindrance of the C-6 methylene group was exploited for the regioselective cleavage of the C-8 methylene group in the ketone **14**. Thus, controlled ozonolysis of the bicyclic ketone **14** in methylene chloride–methanol followed by treatment of the intermediate methoxyhydroperoxide with acetic anhydride, triethylamine and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) in refluxing benzene furnished the keto ester **15**‡ via the Criegee fragmentation,[6,7] along with varying amounts (10–15%) of the simple ozonolysis product. Regioselective hydrogenation using 5% Pd/C as the catalyst in ethyl acetate transformed the enone ester **15** into the saturated ketone **16**. For further elaboration, it was anticipated that the ketone could be converted into the corresponding alcohol and protected. Sodium borohydride reduction of the keto ester **16** in methanol, quite expectedly, generated the *cis*-lactone **17**, m.p. 39–40°C (Scheme 3). The problem was circumvented via the

Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, 0°C, 30 min; (b) 5% NaOH in MeOH:H_2O (1:1), reflux, 12 h; (c) $NaBH_4$, THF, 0°C, 3 h; (d) CH_2N_2, Et_2O, 0°C, 10 min

‡ All the compounds exhibited spectral data consistent with their structures. Yields refer to isolated and chromatographically pure compounds. Spectral data for the bicyclic ketone **14**: $[\alpha]_D^{26}$ –4.9 (*c* 7.32; $CHCl_3$). IR (neat): ν_{max} 1720, 1650, 1630, 890 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.0 (2H, s), 4.93 (1H, br s), 4.79 (1H, br s), 2.68 (1H, dd, *J* 20.4 and 3.9 Hz), 2.41 (2H, t, *J* 2.3 Hz), 2.31 (1H, br s), 2.26 (1H, dd, *J* 20.4 and 2.9 Hz), 1.18 (3H, s), 1.15 (3H, s), 1.14 (3H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 211.3 (s), 156.4 (s), 145.4 (s), 108.6 (t), 108.4 (t), 52.4 (s), 50.1 (d), 40.6 (t), 38.4 (t), 37.4 (s), 31.0 (q), 28.2 (q), 16.2 (q). For the keto ester **15**: $[\alpha]_D^{25}$ +38 (*c* 1.1; $CHCl_3$). IR (neat): ν_{max} 1740, 1680, 1622, 902 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.53 (1H, d, *J* 10.2 Hz), 5.99 (1H, d, *J* 10.2 Hz), 5.16 (1H, s), 5.11 (1H, s), 3.56 (3H, s), 3.35 and 2.76 (2H, 2×d, *J* 16.7 Hz), 1.38 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.30 (3H, s, CH_3). ^{13}C NMR (75 MHz, DEPT): δ 200.1 (C), 171.2 (C), 157.2 (C), 155.8 (CH), 123.9 (CH), 110.4 (CH_2), 51.4 (CH_3), 49.3 (C), 42.7 (CH_2), 37.5 (C), 33.0 (CH_3), 31.2 (CH_3), 30.8 (CH_3). For the tricyclic ketone **25**: m.p. 73–75°C. $[\alpha]_D^{25}$ –25 (*c* 1.0; $CHCl_3$). IR (neat): ν_{max} 1715, 889 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.15 (1H, dd, *J* 11.3 and 4.4 Hz), 2.12 and 1.74 (2H, 2×d, *J* 18.0 Hz), 1.90–1.40 (5H, m), 1.37 (3H, s), 1.15 (3H, s), 1.11 (3H, s), 1.03 (1H, d, *J* 4.8 Hz), 0.86 (9H, s), 0.82 (3H, s), 0.03 (6H, s). ^{13}C NMR (75 MHz, DEPT): δ 213.2 (C), 76.9 (CH), 48.5 (C), 44.7 (CH_2), 44.2 (C), 41.4 (C), 38.3 (CH_2), 33.6 (C), 28.9 (CH_3), 28.6 (CH_3), 27.7 (CH_2), 25.8 (3 C, CH_3), 21.3 (CH_2), 18.5 (CH_3), 18.0 (C), 14.2 (CH_3), –3.7 (CH_3), –5.0 (CH_3). For the thapsenyl TBDMS ether **27**: $[\alpha]_D^{25}$ +27 (*c* 1.2; $CHCl_3$). IR (neat): ν_{max} 1652, 888 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.84 (1H, s), 4.79 (1H, s), 3.42 (1H, dd, *J* 11.2 and 4.4 Hz), 2.70 (1H, m), 2.35 and 2.15 (2H, 2×d, *J* 16.2 Hz), 1.66–1.55 (3H, m), 1.20 (1H, dd, *J* 10.2 and 3.6 Hz), 1.07 (3H, d, *J* 7.0 Hz), 0.98 (3H, s), 0.96 (3H, s), 0.88 (9H, s), 0.86 (3H, s), 0.82 (3H, s), 0.01 (6H, s). ^{13}C NMR (75 MHz, DEPT): δ 156.5 (C), 106.3 (CH_2), 73.0 (CH), 50.9 (C), 49.3 (C), 44.4 (CH_2), 42.6 (CH), 37.1 (CH_2), 36.2 (C), 29.9 (CH_3), 27.9 (CH_2), 26.1 (3 C, CH_3), 25.5 (CH_3), 18.5 (CH_3), 18.2 (CH_3), 15.9 (CH_3), 13.8 (CH_3), –3.7 (CH_3), –4.7 (CH_3).

intramolecular reduction of the ketone group. Consequently, hydrolysis of the keto ester **16** generated the keto acid **18**. Treatment of the keto acid **18** with sodium borohydride in THF delivered the hydride in an intramolecular fashion via the carboxyborohydride and generated the hydroxy acid **19**, which on esterification with diazomethane furnished the hydroxy ester **20**, along with trace amounts of the *cis*- and *trans*-lactones **17** and **21**. The alcohol group in the hydroxy ester **20** was protected as its *tert*-butyldimethylsilyl (TBDMS) ether **22** by treatment with TBDMSCl and DMAP in DMF. The third quaternary carbon atom was created employing an intramolecular diazoketone cyclopropanation reaction. Base-catalysed hydrolysis of the ester moiety in **22** furnished the acid **23**. To introduce simultaneously a methyl group at the C-9 position of thapsane, it was intended to convert the acid **23** into the diazoketone **24**. Consequently, reaction of the acid **23** with oxalyl chloride in benzene and pyridine followed by treatment of the resulting acid chloride with an excess of ethereal diazoethane furnished the diazoketone **24**. Anhydrous copper sulfate–copper-catalysed decomposition of the diazoketone **24** in refluxing cyclohexane under irradiation with a tungsten lamp followed by stereospecific insertion of the resulting keto carbenoid furnished the tricyclic ketone **25**,‡ containing four quaternary centres. Regiospecific cleavage of the cyclopropane ring[2,8] employing lithium in liquid ammonia reduction conditions transformed the tricyclic ketone **25** into northapsanone **26** in a stereoselective manner. The fifteenth carbon atom of thapsane was introduced employing a Wittig olefination. Thus, reaction of the ketone **26** with methylenetriphenylphosphorane in benzene at 70°C furnished the TBDMS ether of thaps-8(11)-en-5-ol (+)-**27**.‡ Isomerisation of the double bond with p-TSA transformed **27** into the TBDMS ether of thaps-8-en-5-ol (–)-**28**. Finally, cleavage of the TBDMS ether **28** with tetrabutylammonium fluoride (TBAF) in refluxing THF furnished (–)-thaps-8-en-5-ol **29**, m.p. 77–79°C, $[\alpha]_D^{26}$ –15.2 (*c* 1.2; $CHCl_3$).

In conclusion, we have developed the first enantiospecific approach to chiral thapsanes. A combination of an intramolecular alkylation and a facile Crigee fragmentation reaction were exploited for the translocation of the isopropenyl group of carvone from C-5 to the C-2 position, thereby incorporating nine of the 10 carbons of carvone in thapsane. An intramolecular diazoketone cyclopropanation reaction was employed for the generation of three contiguous quaternary carbon atoms. Currently, we are investigating extension of this methodology to natural thapsanes.

Acknowledgements

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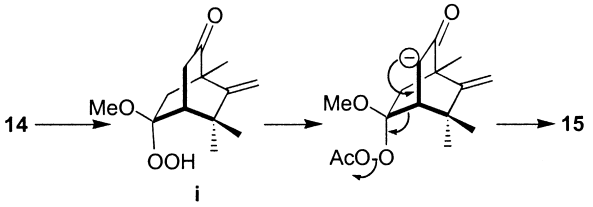
7. The stereochemistry of the hydroperoxy group in the ozonolysis product **i** is ideally suited for a facile fragmentation in preference to rearrangement, as depicted below.



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