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Synthesis of Chiral Bicyclo[4.3.1]decanes *via* an Intramolecular Carbonyl Ene-reaction[1]

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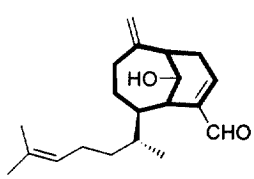
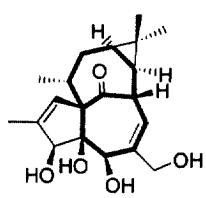
Abstract: Synthesis of chiral bicyclo[4.3.1]decanes via an intramolecular acid catalysed type II ene reaction of chiral (5-isopropenylcyclohex-2-enyl)acetaldehydes derived from (*R*)-carvone is described.

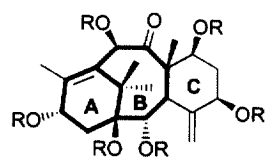
Bridged medium-ring systems are commonly encountered in natural products, in particular in terpenoids. For example, the diterpenes sanadaol[2] **1**, ingenanes[3] **2** and taxanes[4] **3** comprise bicyclo[4.3.1]decane, bicyclo-[4.4.1]undecane and bicyclo[5.3.1]undecane systems, respectively, as part structures. During our studies enroute to chiral taxanes from carvone **4**,[5] we envisaged a strategy for the construction of the AB ring system of taxanes *via* ring-expansion of bicyclo[4.3.1]decanes to bicyclo[5.3.1]undecanes. In this context, we developed an efficient route for the construction of chiral bicyclo[4.3.1]decanes employing an acid-catalysed intramolecular type II carbonyl ene reaction,[6] which is the subject of this communication.



Sanadaol (**1**)

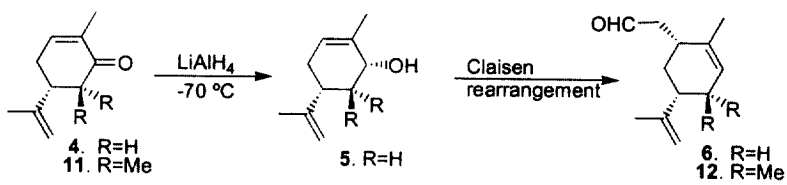


Ingenol (**2**)



Taxanes (**3**)

It was anticipated that introduction of an acetaldehyde side chain at the C-1 position of carvone *syn* to the isopropenyl group would provide a suitable starting material for exploring an intramolecular carbonyl ene reaction for the generation of chiral bicyclo[4.3.1]decanes. The Claisen rearrangement was chosen for the stereoselective introduction of the acetaldehyde side chain. Thus, stereoselective reduction of (*R*)-carvone **4** with lithium aluminium hydride furnished the *syn* allylic alcohol **5**.[7] A one pot Claisen rearrangement of carveol **5** with ethyl vinyl ether in the presence of a catalytic amount of mercuric acetate in a sealed tube at 180 °C for 48 h stereo-specifically furnished the aldehyde[8] **6** in 84% yield. Treatment of a 0.005 M methylene chloride solution of the aldehyde **6** at 0-5 °C with 0.5 equivalents of boron trifluoride etherate for seven minutes furnished a 2.3:1 mixture of the *endo* and *exo* alcohols[8] **7a** and **7b** in 87% yield which was separated by silica gel column chromatography.



4. R=H
11. R=Me

5. R=H

6. R=H
12. R=Me

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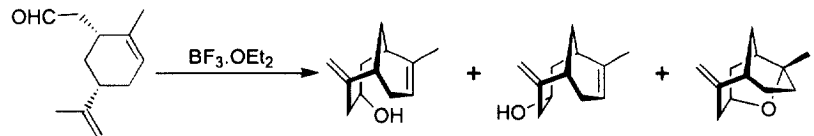
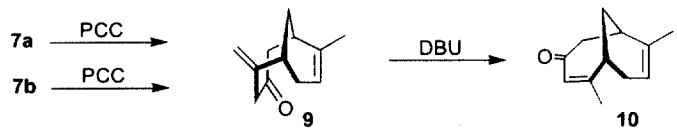
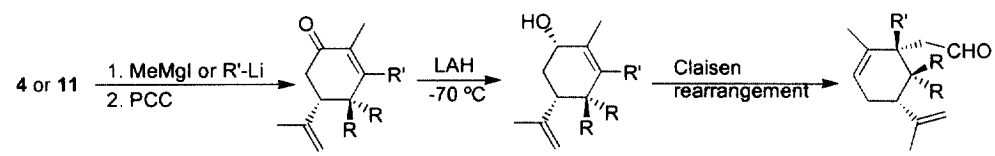


The structures of the alcohols **7a** and **7b** were established from their spectral data.[8] Interestingly, increasing the amount of boron trifluoride etherate to 1.1 equivalents generated the ether[8] **8** in addition to the two alcohols **7a** and **7b**, in the ratio 1.1:1:1.1 (80%). Formation of the ether **8** at the expense of the *endo* alcohol **7a**, established the *endo* stereochemistry of the alcohol **7a**. Oxidation of the alcohols **7a** and **7b** with pyridinium chlorochromate (PCC) in methylene chloride furnished the ketone[8] **9**, which on isomerisation with 1,8-diazabicyclo-[5.4.0]undecane (DBU) in methylene chloride furnished the conjugated enone[8] **10**. It is worth noting that the compounds **7**, **9** and **10** contain the bicyclic carbon framework of sanadaol[2] **1** (except the eight carbon side chain at C-2), and are antipodal to the natural product.



To test the generality of the methodology, (*R*)-carvone **4** was transformed into several aldehydes analogous to **6** which were subjected to the intramolecular carbonyl ene reaction. Thus, stereoselective reduction of dimethyl-carvone[5] **11** followed by a Claisen rearrangement furnished the aldehyde **12**.[9] 1,3-Alkylative enone transposition[10] followed by stereoselective reduction transformed carvone **4** into the allyl alcohols **13a-e**. Claisen rearrangement of the alcohols **13a-e** furnished the aldehydes **14a-e**.[9] The same sequence of reactions on dimethylcarvone **11** generated the aldehyde **15**.[9] Treatment of the aldehydes **12**, **14a-e** and **15** with boron trifluoride etherate in methylene chloride (0.005 M) at 0-5 °C cleanly furnished the *endo* and *exo* bicyclo[4.3.1]decanols **16**, **17a-e** and **18**. PCC oxidation followed by DBU catalysed isomerisation of the resultant ketones **19**, **20a-e** and **21** transformed the alcohols **16**, **17a-e** and **18** into the enones **22**, **23a-e** and **24**. The results are summarised in the Table. The reactions are very facile and no traces of side products were noticed even with the aldehydes **14c,d** containing an aromatic ring ideally suited for cyclisation. Similarly no competition was observed with the butenyl side chain in the aldehyde **14b**.



Thermal activation (sealed tube, toluene, 150 °C, 4 days) of the aldehyde **15** in the presence of a trace amount of propionic acid also furnished the alcohol **18** in 87% yield (35% conversion), which is ideally suited for further elaboration to AB ring system of taxanes via ring expansion. However, in contrast the aldehyde **14a**, with no gem dimethyl group, failed to undergo the intramolecular ene reaction under identical conditions even after a prolonged reaction time.

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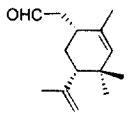
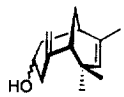
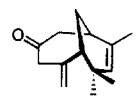
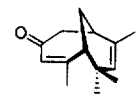
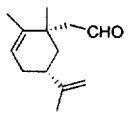
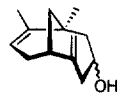
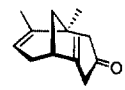
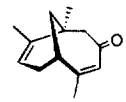
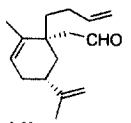
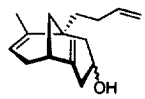
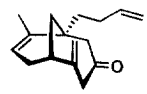
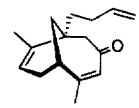
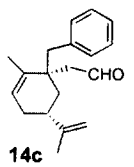
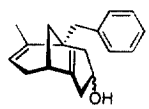
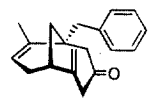
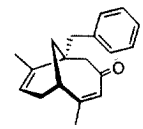
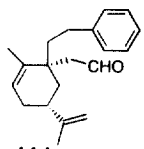
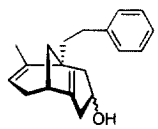
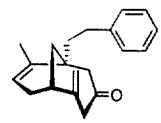
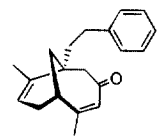
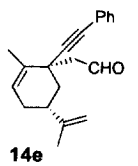
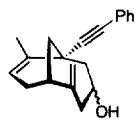
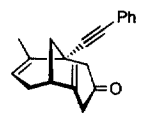
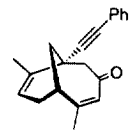
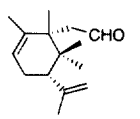
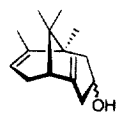
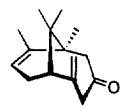
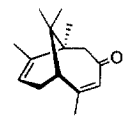
Table: Synthesis of chiral bicyclo[4.3.1]decanes[8]

Entry	Aldehyde	ene product (*endo*:*exo*), yield	oxidation product, yield	enone, yield
(a)	**6**	**7** (2.3:1), 87%	**9** 75%	**10** 95%
(b)	 **12**	 **16** (1:0), 83%	 **19** 81%	 **22** 95%
(c)	 **14a**	 **17a** (7.5:1), 75%	 **20a** 92%	 **23a** 83%
(d)	 **14b**	 **17b** (15:1), 95%	 **20b** 90%	 **23b** 92%
(e)	 **14c**	 **17c** (7.7:1), 86%	 **20c** 98%	 **23c** 83%
(f)	 **14d**	 **17d** (2.9:1), 66%	 **20d** 85%	 **23d** 92%
(g)	 **14e**	 **17e** (1:0), 70%	 **20e** 85%	 **23e** 78%
(h)	 **15**	 **18** (1:0), 85%	 **21** 67%	 **24** 83%

References and Notes

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8. Yields refer to isolated and chromatographically pure compounds. The isomer ratios are based on the isolated compounds. All the compounds exhibited spectral data consistent with their structures. Optical rotation, IR, ^{1}H and ^{13}C NMR spectra of selected compounds are as follows: For the aldehyde **6**: $[\alpha]_D^{24}$: 54 (c 2.4, $CHCl_3$). IR (neat): ν_{max} 2720, 1720, 1640, 890 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (1 H, t, J=2.5 Hz, H-C=O), 5.53 (1 H, brs, olefinic H), 4.71 (1 H, s) and 4.69 (1 H, s) [C=CH_2], 2.73 (1 H, brs), 2.66 (1 H, dd, J=16.2 and 1.8 Hz), 2.34 (1 H, ddd, J=16.2, 8.1 and 2.4 Hz), 1.75-2.25 (4 H, m), 1.72 (3 H, s) and 1.66 (3 H, s) [2 x olefinic CH_3], 1.25 (1 H, q, J=12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 202.3 (CH, *HC*=O), 149.0 (C, *C*=CH_2), 133.8 (C, C-2), 123.8 (CH, C-3), 108.6 (CH_2, C=*C*H_2), 47.3 (CH_2), 41.0 (CH), 35.3 (CH_2, C-4), 35.1 (CH), 30.7 (CH_2, C-6), 20.9 (CH_3) and 20.4 (CH_3) [2 x olefinic CH_3]. For *endo* 9-methyl-5-methylenebicyclo[4.3.1]dec-8-en-3-ol **7a**: $[\alpha]_D^{26}$: - 42 (c 1.8, $CHCl_3$). IR (neat): ν_{max} 3380, 1620, 885 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.37 (1 H, brs, H-8), 5.14 (1 H, s) and 5.05 (1 H, s) [C=CH_2], 4.01 (1 H, brs, C*H*-OH), 2.75 (1 H, brs), 2.66 (1 H, d, J=13.5 Hz) and 2.60 (1 H, dd, J=13.5 and 6.5 Hz) [H-4], 2.35 (3 H, brs), 2.25 (1 H, brs), 1.80-2.10 (2 H, m), 1.77 (3 H, s, olefinic CH_3), 1.52 (1 H, td, J=14.4 and 4.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 148.9 (C, C-5), 138.5 (C, C-9), 121.5 (CH, C-8), 116.2 (CH_2, C=*C*H_2), 70.1 (CH, CH-OH), 43.0 (CH_2), 39.0 (CH_2), 35.5 (CH) and 33.7 (CH) [C-1 and 6], 33.1 (CH_2), 31.7 (CH_2), 22.3 (CH_3). For the *exo* alcohol **7b**: $[\alpha]_D^{26}$:-26 (c1.0, $CHCl_3$). IR (neat): ν_{max} 3340, 1625, 890 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.4 (1 H, brs, H-8), 4.98 (1 H, s) and 4.95 (1 H, s) [C=CH_2], 3.50 (1 H, m, C*H*OH), 2.70 (1 H, brs), 1.30-2.60 (9 H, m), 1.67 (3 H, s, olefinic CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 151.2 (C, C-5), 134.9 (C, C-9), 122.2 (CH, C-8), 113.8 (CH_2, C=*C*H_2), 70.9 (CH, C-3), 46.9 (CH_2), 41.3 (CH_2), 34.1 (CH_2), 33.7 (2 C, CH, C-1 and 6), 31.1 (CH_2, C-10), 21.9 (CH_3). For the ether **8**: $[\alpha]_D^{25}$: -37 (c 1.86, $CHCl_3$). IR (neat): ν_{max} 1625, 885 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (1 H, t, J=2.1 Hz) and 4.57 (1 H, t, J=2.1 Hz) [C=CH_2], 4.30-4.50 (1 H, m, CH-O), 2.78 (1 H, d, J=ca.15 Hz), 2.75 (1 H, brs), 2.25-2.40 (2 H, m), 2.12 (1 H, dd, J=8.4 and 6.3 Hz), 1.8-2.0 (1 H, m), 1.40-1.80 (5 H, m), 1.27 (1 H, dd, J=12.3 and 3 Hz), 1.19 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 153.5 (C, *C*=CH_2), 112.0 (CH_2, C=*C*H_2), 81.8 (C, C-O), 76.4 (CH, CH-O), 42.3 (CH_2), 41.3 (CH), 36.6 (CH), 36.3 (CH_2), 34.3 (CH_2), 30.6 (CH_2), 29.9 (CH_3), 19.8 (CH_2). For the ketone **9**: $[\alpha]_D^{26}$: -125 (c 1.3, $CHCl_3$). IR (neat): ν_{max} 1690, 1625, 890 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.51 (1 H, brs, H-8), 4.97 (1 H, s) and 4.76 (1 H, s) [C=CH_2], 3.29 (1 H, d, J=16.5 Hz) and 3.03 (1 H, d, J=16.5 Hz) [H-4], 2.89 (1 H, m), 2.74 (1 H, dd, J=15.9 and 6 Hz), 2.61 (1 H, dd, J=15.7 and 3 Hz), 2.43 (1 H, m of d, J=ca.15Hz), 2.33 (1 H, brs), 2.13 (1 H, t of d, J=13.2 and 5 Hz), 1.97 (1 H, m of d, J= ≈18 Hz), 1.88 (1 H, d, J=11 Hz), 1.68 (3 H, s, olefinic CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 210.3 (C, C=O), 147.6 (C, C-5), 135.9 (C, C-9), 122.1 (CH, C-8), 114.8 (CH_2, C=*C*H_2), 49.5 (CH_2, C-4), 47.2 (CH_2, C-2), 37.6 (CH), 36.4 (CH_2, C-7), 32.9 (CH), 29.6 (CH_2), 22.3 (CH_3). For the enone **10**: m.p.: 55-56 °C. $[\alpha]_D^{26}$: -14.5 (c 1.1, $CHCl_3$). IR (neat): ν_{max} 1640 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88 (1 H, s, H-4), 5.34 (1 H, d, J=3.9 Hz, H-8), 2.93 (1 H, dd, J=16.4 and 4.5 Hz, H_{2a}), 2.70 (1 H, td, J=6.6 and 3.3 Hz, H-6), 2.59 (1 H, dd, J=16.4 and 4.0 Hz, H_{2b}), 2.42 (1 H, m of d, J=15 Hz, H_{7a}), 2.3 (1 H, brs, H-6), 2.15 (2 H, t, J=3.9 Hz, H-10), 1.99 (1 H, dd, J=15 and 5.1 Hz), 1.97 (3 H, s, C_5-CH_3), 1.69 (3 H, s, C_9-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 202.1 (C, C=O), 157.3 (C, C-5), 134.4 (C, C-9), 129.8 (CH, C-4), 119.5 (CH, C-8), 47.8 (CH_2, C-2), 38.2 (CH, C-6), 32.5 (CH_2, C-7), 32.3 (CH, C-1), 29.9 (CH_2, C-10), 27.5 (CH_3, C_5-CH_3), 21.8 (CH_3, C_9-CH_3).
9. For convenience most of the aldehydes were also prepared employing an ortho ester Claisen rearrangement of the corresponding allyl alcohols followed by conversion of the resultant ester group into the aldehyde via reduction oxidation protocol.
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