Competitive formation of spiro[5.5]undecane in preference to bicyclo[4.3.1]decane via type II carbonyl ene reaction

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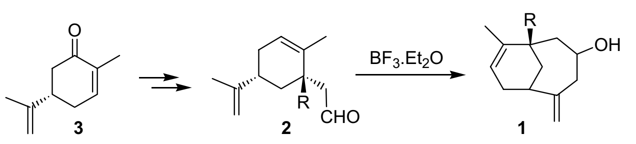
Abstract—The presence of an isopropenyl group at the C-1 position of a 3-isopropenylcyclohexaneacetaldehyde failed to generate the spiro[4.5]decane and produced only bicyclo[4.3.1]decanol. However, the presence of a methallyl group at the C-1 position of 3-isopropenylcyclohexaneacetaldehyde generated exclusively the spiro[5.5]undecanols.

1. Introduction

Intramolecular ene reactions in which a carbonyl group serves as the enophile (commonly referred as carbonyl ene reactions[1]) have been widely used in synthesis for the construction of five-, six- and seven-membered rings. As in Diels–Alder reactions, Lewis acid catalysis via complexation with the carbonyl group increases the rate of the reactions making them useful in natural product synthesis.[1] A cyclohexane ring containing acetaldehyde and isopropenyl side chains at the 1,3-positions in a *cis* orientation was found to be the ideal precursor for the synthesis of bicyclo[4.3.1]decanes via a carbonyl ene reaction. The enantioselective syntheses of several bicyclo[4.3.1]decanes **1** have been accomplished[2] in an efficient manner starting from aldehydes **2**, which were obtained from the readily and abundantly available monoterpene (*R*)-carvone **3**.



R = H; Me; CH_2Ph; CH_2CH_2Ph;$CH_2CH_2CH{=}CH_2$; C≡CPh

The presence of spiro fused systems, either simple or as part of a polycyclic carbon framework is commonly encountered in many natural products.[3] In this context, it was decided to investigate the type II carbonyl ene reaction of aldehyde **4**. Since aldehyde **4** contains two isopropenyl groups at the C-1 and C-3 positions of a cyclohexaneacetaldehyde, one would lead to bi-cyclo[4.3.1]decane and the other to spiro[4.5]decane. This is an interesting precursor for assessing the utility of carbonyl ene reactions for the generation of a bridge system versus a spiro system.

2. Results and discussion

Aldehyde **4** was prepared from (*R*)-carvone **3** (Scheme 1). An alkylative enone transposition[4] was employed for the generation of 3-isopropenylcarvone **6**. Thus, the regioselective 1,2-addition of isopropenylmagnesium bromide to carvone **3** in THF followed by oxidation of the resultant tertiary bi-allylic alcohol **5** with a mixture of PCC and silica gel in methylene chloride cleanly generated the transposed dienone **6**. Regioselective reduction of dienone **6** with LAH in ether at low temperature (−70 °C) furnished the *syn* allyl alcohol **7**, in a highly stereoselective (>97%) manner, in which the stereochemistry of the allyl alcohol was assigned on the basis of the well established reduction of 5-substituted cyclohexenones.[5] The *ortho*-ester Claisen rearrangement[6] of allyl alcohol **7** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180 °C furnished ester **8** in a stereoselective manner. Reduction of ester **8** with LAH followed by oxidation of the resultant primary alcohol with PCC and silica gel in methylene chloride furnished aldehyde **4**.

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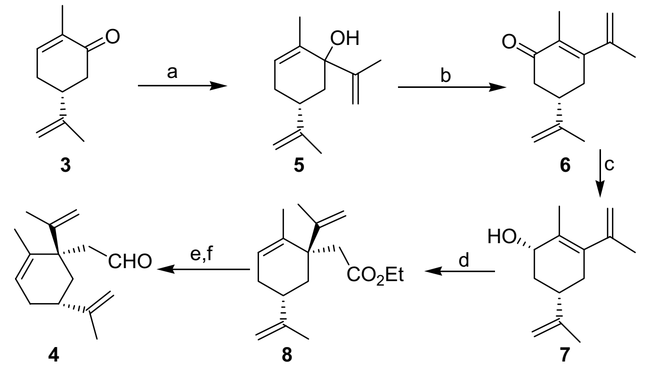
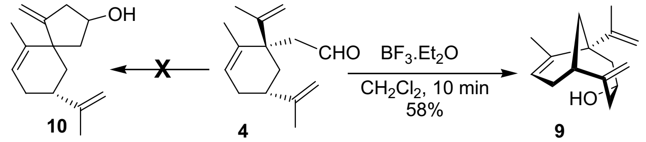
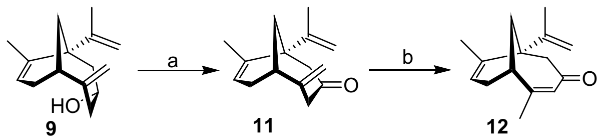


Scheme 1. Reagents, conditions and yields: (a) $CH_2{=}C(Me)MgBr$, THF, rt, 4 h; (b) PCC, silica gel, CH_2Cl_2, rt, 6 h; 63% (for two steps); (c) $LiAlH_4$, Et_2O, −70 °C, 2 h, 90%; (d) $MeC(OEt)_3$, $EtCO_2H$, sealed tube, 180 °C, 4 days, 70%; (e) $LiAlH_4$, Et_2O, 0 °C, 0.5 h, 92%; (f) PCC, silica gel, CH_2Cl_2, rt, 2 h, 81%.

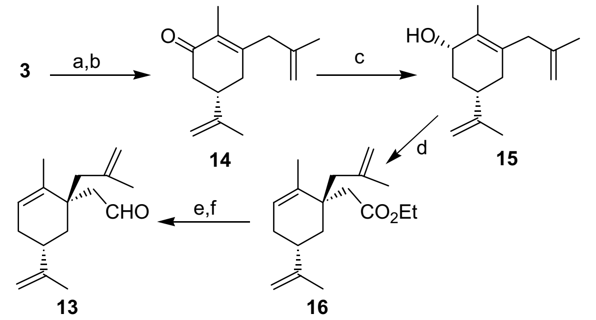


Treatment of a 0.005 M solution of aldehyde **4** in methylene chloride with 0.5 equiv of boron trifluoride diethyl etherate at 5 °C for 10 min unexpectedly furnished only the *endo*-bicyclo[4.3.1]decenol **9** in a highly stereoselective (>95% by NMR) manner with no detectable amounts of the spiro[4.5]decane **10** being formed. The structure of alcohol **9** was established from its spectral data, and further confirmed by the oxidation of alcohol **9** with PCC and sodium acetate in methylene chloride to furnish ketone **11**. Isomerisation of the exomethylene group in **11** with a catalytic amount of DBU in methylene chloride furnished the conjugated ketone **12**.[9]



(a) PCC, NaOAc, CH_2Cl_2, rt, 0.5 h, 82%; (b) DBU, CH_2Cl_2, rt, 3 h, 83%.

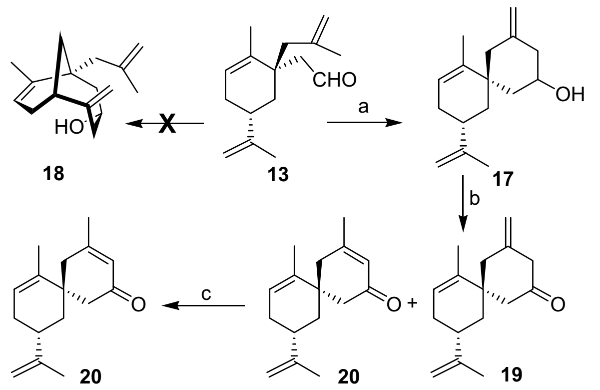
Even though it is known that 3-methylenecyclopentanols could be generated from γ,δ-unsaturated aldehydes via a Lewis acid catalysis, the reaction is supposed to proceed via a zwitterion mechanism,[1b] as the transition state for the concerted type II ene reaction is very strained, which explains the failure of the formation of the spiro system **10** from the aldehyde **4**. To substantiate further, we turned our attention towards the homologous system **13**, which could generate either the bicyclo[4.3.1]decane or the spiro[5.5]undecane via the type II carbonyl ene reaction. Accordingly, the methallyl group was chosen in place of the isopropenyl group



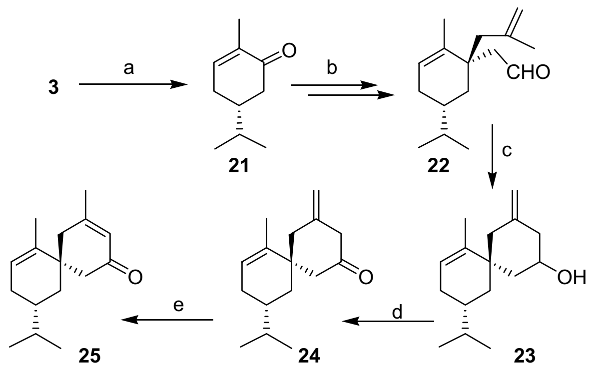
Scheme 2. Reagents, conditions and yields: (a) $CH_2{=}C(Me)$-CH_2MgCl, THF, rt, 8 h; (b) PCC, silica gel, CH_2Cl_2, rt, 8 h; 65% (for two steps); (c) $LiAlH_4$, Et_2O, −70 °C, 2 h, 95%; (d) $MeC(OEt)_3$, $EtCO_2H$, sealed tube, 180 °C, 3 days, 60%; (e) $LiAlH_4$, Et_2O, 0 °C, 1 h, 90%; (f) PDC, CH_2Cl_2, rt, 2 h, 94%.

(Scheme 2). Thus, a 1,2-addition of methallylmagnesium chloride to carvone **3** in THF at 0 °C followed by oxidation of the resultant alcohol with a mixture of PCC and silica gel in methylene chloride at room temperature generated enone **14**. Stereo- and regioselective reduction of enone **14** with LAH followed by an *ortho*-ester Claisen rearrangement of allyl alcohol **15** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180 °C for 4 days generated ester **16**. Reduction of ester **16** with LAH followed by oxidation of the primary alcohol with pyridinium dichromate (PDC) in methylene chloride furnished aldehyde **13**. Treatment of a 0.005 M solution of the aldehyde **13** in methylene chloride at 0–5 °C with 0.5 equiv of boron trifluoride diethyl etherate for 10 min furnished exclusively[7] the spiro[5.5]undecanol **17** (Scheme 3). Comparison of the spectral data (IR, ^1H and ^{13}C NMR) with that of bicyclo[4.3.1]decanes **1** and **9** confirmed that the product formed is the spiro alcohol **17** and not **18**. Oxidation of alcohol **17** with PCC and silica gel in methylene chloride furnished a mixture of ketone **19** and conjugated enone **20**, which on treatment with a catalytic amount of DBU in methylene chloride at room temperature furnished the conjugated ketone **20**.

To further establish the strategy for the enantioselective synthesis of spiro[5.5]undecanes, the sequence was also carried out with dihydrocarvone **21**. Thus, partial hydrogenation of (*R*)-carvone **3** with Wilkinson's catalyst[8] in benzene at one atmospheric pressure furnished dihydrocarvone **21**, which was transformed into aldehyde **22**. Treatment of a 0.005 M solution of aldehyde **22** in methylene chloride at 0–5 °C with 0.5 equiv of boron trifluoride diethyl etherate for 10 min furnished, as expected, the spiro[5.5]undecanol **23**.[7] Oxidation of alcohol **23** with PCC and silica gel in methylene chloride furnished ketone **24**, which on isomerisation with a cat-



Scheme 3. Reagents, conditions and yields: (a) $BF_3 \cdot Et_2O$, CH_2Cl_2, 5 °C, 10 min, 43%; (b) PCC, silica gel, CH_2Cl_2, rt, 2 h; (c) DBU, CH_2Cl_2, rt, 2 h, 85% (two steps).



Scheme 4. Reagents, conditions and yields: (a) $(Ph_3P)_3RhCl$, C_6H_6, H_2, 1 atm, rt, 2 days, 98%; (b) as in Scheme 2; (c) $BF_3 \cdot Et_2O$, CH_2Cl_2, 5 °C, 10 min, 60%; (d) PCC, silica gel, CH_2Cl_2, rt, 2 h; 83%; (e) DBU, CH_2Cl_2, rt, 3 h, 92%.

alytic amount of DBU in methylene chloride furnished spirodienone **25** (Scheme 4).

3. Conclusion

In conclusion, we have demonstrated that the formation of a spiro[4.5]decanol cannot compete with the formation of bicyclo[4.3.1]decane via a type II carbonyl ene reaction of a 1,3-diisopropenylcyclohexaneacetaldehyde. However, under the same conditions, 1-(2-methylallyl)-3-isopropenylcyclohexaneacetaldehyde exclusively generates the spiro[5.5]undecane. Currently, we are investigating the potential of this reaction for the enantioselective synthesis of natural products containing a spiro system.

Acknowledgements

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7. The ene reaction was found to be highly stereoselective (>95% by ^1H and ^{13}C NMR). However, since the next step is oxidation, no attempt was made to assign the stereochemistry of alcohols **17** and **23**.
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9. All the compounds exhibited the spectral data (IR, ^1H and ^{13}C NMR and mass) consistent with the structures. Yields refer to isolated and chromatographically pure compounds. Selected spectral data for the bicyclic enone **12**: $[\alpha]_D^{24} = -220$ (*c* 0.5, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1666, 902. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.87 (1H, s), 5.44 (1H, d, $J = 5.1$ Hz), 4.80 (1H, s), 4.75 (1H, s), 2.93 and 2.64 (2H, AB q, $J = 15.0$ Hz), 2.68 (1H, s), 2.50–2.30 (1H, m), 2.17 (1H, t of d, $J = 13.8$ and 3.5 Hz), 2.05–1.90 (2H, m), 1.96 (3H, s), 1.65 (3H, s), 1.48 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 200.0 (C), 155.3 (C), 150.0 (C), 135.8 (C), 130.0 (CH), 121.8 (CH), 111.5 (CH_2), 53.0 (CH_2), 42.8 (C), 38.7 (CH_2), 38.5 (CH), 30.1 (CH_2), 27.4 (CH_3), 19.1 (CH_3), 19.0 (CH_3). Mass: *m/z* 215 (M-1, 5%), 119 (25), 117 (20), 107 (30), 91 (35), 43 (100). For the spiroenone **20**: $[\alpha]_D^{22} = +44.2$ (*c* 1.2, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1660, 1645, 885. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.81 (1H, br s), 5.44 (1H, d, $J = 5.2$ Hz), 4.62 (1H, s), 4.60 (1H, s), 2.62 (1H, d, $J = 15.6$ Hz), 2.49 (1H, d, $J = 18.6$ Hz), 2.00–1.70 (6H, m), 1.88 (3H, s), 1.64 (3H, s), 1.62 (3H, s), 1.12 (1H, t, $J = 12.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 198.9 (C), 158.8 (C), 148.7 (C), 136.9 (C), 125.7 (CH), 125.2 (CH), 109.5 (CH_2), 48.4 (CH_2), 41.2 (C), 39.3 (CH_2), 37.9 (CH), 37.5 (CH_2), 31.3 (CH_2), 24.7 (CH_3), 20.7 (CH_3), 19.3 (CH_3). For the spiroenone **25**: $[\alpha]_D^{24} = +64.0$ (*c* 0.8, $CHCl_3$). IR (neat): ν_{max}/cm^1 1670. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.86 (1H, br s), 5.47 (1H, d, $J = 4.8$ Hz), 2.66 (1H, d, $J = 15.6$ Hz), 2.51 and 2.12 (2H, 2 × d, $J = 18.6$ Hz), 2.10–1.80 (3H, m), 1.93 (3H, s), 1.75–1.55 (2H, m), 1.62 (3H, s), 1.39 (1H, septet, $J = 6.6$ Hz), 0.90 (1H, d of t, $J = 12.5$ and 1.5 Hz), 0.83 (6H, d, $J = 6.6$ Hz).^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 199.2 (C), 159.0 (C), 137.0 (C), 125.6 (CH), 125.5 (CH), 48.5 (CH_2), 41.1 (C), 39.3 (CH_2), 36.8 (CH), 36.2 (CH_2), 32.2 (CH), 29.5 (CH_2), 24.6 (CH_3), 20.0 (CH_3), 19.5 (CH_3), 19.2 (CH_3). Mass: *m/z* 232 (M^+, $C_{16}H_{24}O$, 30%), 189 (17), 161 (18), 150 (30), 135 (40), 121 (30), 107 (100), 93 (60), 91 (60).