Terpenes to Terpenes. Stereo- and Enantio-selective Synthesis of (+)-α-Elemene and a Short Route to a Versatile Diquinane Chiron

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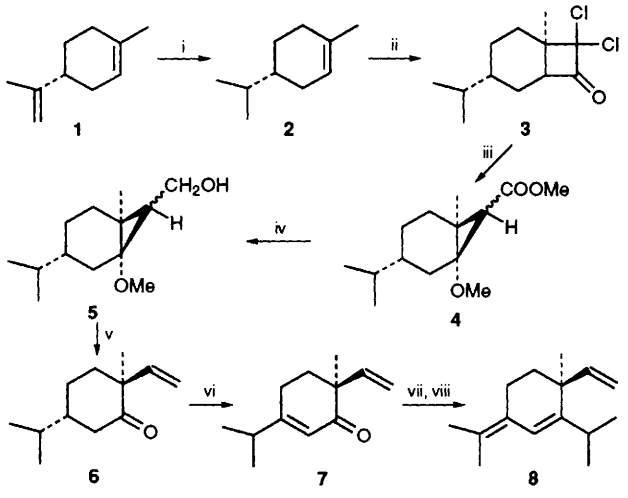
Syntheses of sesquiterpene (+)-α-elemene from monoterpenes (+)-limonene and (+)-2-carene following a new strategy are reported.

Terpenes as chirons have an intrinsic advantage over other natural products in the 'chiral pool', as they are amenable to restructuring into cyclic and acyclic fragments that can be directly incorporated into the carbocyclic framework of complex target structures. We[1a,b,i] and many others[1c–h] have shown the efficacy of this approach using monoterpenes for synthesizing sesquiterpenes, for instance. Herein, we report an approach using the C_{10}-monoterpenes (+)-limonene **1** and (+)-2-carene **9** to prepare the C_{15}-elemane skeleton. We also report the conversion of these monoterpenes to the diquinane chiron **15** for use in synthesizing diverse polyquinane natural products.

Addition of dichloroketene to (+)-dihydrolimonene **2**, under ultrasound irradiation,[2] proceeded stereoselectively to give the [2 + 2] adduct **3**.† Sodium methoxide-mediated ring contraction of **3** occurred smoothly to furnish bifunctional 'push-pull' cyclopropane ester **4** (mixture of *exo* and *endo* isomers).[3,4] Dibal-H reduction of **4** led to the cyclopropylcarbinol **5**, again as a mixture of *exo* and *endo* isomers but no separation was required. Brief exposure of **5** to iodotrimethylsilane resulted in a facile fragmentation *via* cyclopropylcarbinylhomoallylic rearrangement and the (+)-C_{12}-α-vinylketone **6**† was obtained as a single stereoisomer in quantitative yield.[5] On dehydrogenation with SeO_2, **6** gave the enone **7**.† Addition of 2-propyllithium to **7** and dehydration furnished (+)-α-elemene **8**,† identical with the natural product, Scheme 1, and constitutes its first enantioselective synthesis.[6,7]



Scheme 1 *Reagents and conditions*: i, H_2/PtO_2, EtOH, 90%; ii, CCl_3COCl, Zn, Et_2O, ultrasound, 65%; iii, NaOMe–MeOH, heat, 91%; iv, Dibal-H, CH_2Cl_2, −40 °C, 80%; v, Me_3SiI, MeCN, room temp., quant.; vi, SeO_2, Bu^{t}OH, heat, 45%; vii, 2-propyllithium, THF, ultrasound; viii, *p*-TsCl, $CHCl_3$, room temp., 42%

The elemane skeleton, particularly (+)-α-elemene **8** was also synthesized more efficiently from (+)-2-carene **9**, Scheme 2, following protocols similar to those employed for (+)-dihydrolimonene **2**. Thus, addition of dichloroketene to **9** gave exclusively the [2 + 2] adduct **10** which was rearranged[3,4] to the bifunctional cyclopropane **11** (mixture of isomers). LAH reduction to **12** and brief exposure to $ISiMe_3$ yielded the enone **7** through cyclopropylcarbinyl-homoallylic rearrangement followed by concomitant cleavage of the second cyclopropane ring and isomerization of the double bond into conjugation; all in one pot. Enone **7** was further transformed to **8** as described above to furnish (+)-α-elemene **8**.

The ready availability of the α,β-unsaturated enone **7** from both limonene **1** and 2-carene **9**, prompted us to convert it through a [2 + 2] photocycloaddition–fragmentation strategy. **7** underwent smooth intramolecular photocycloaddition to give the tricyclic compound **13**† bearing a bicyclo[2.1.1]hexane moiety. Exposure of **13** to $BF_3{\cdot}Et_2O$ resulted in a smooth regiospecific fragmentation to give the *cis*-diquinane **14** endowed with an angular methyl group. The isopropylidene group in **14** could be cleaved through either ozonolysis or catalytic ruthenium oxidation to deliver the bifunctional (+)-*cis*-diquinane dione **15**,† Scheme 3. The chiral dione **15** with its secured stereochemistry and strategic placement of functionality in the two rings is a promising starting point for further polyquinane synthesis.

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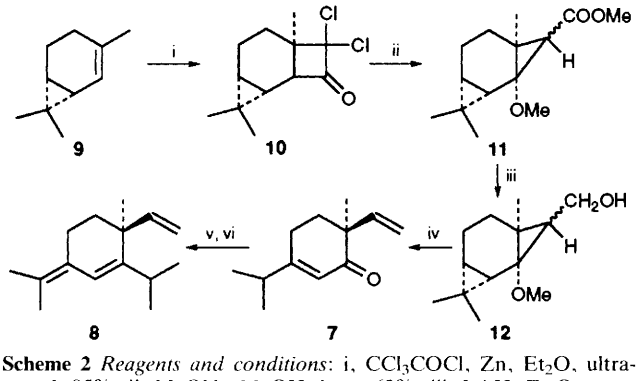
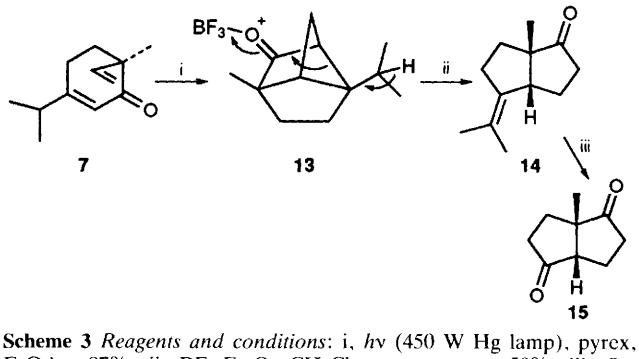


Scheme 2 *Reagents and conditions*: i, CCl_3COCl, Zn, Et_2O, ultrasound, 95%; ii, MeONa–MeOH, heat, 63%; iii, LAH, Et_2O, room temp. 92%; iv, Me_3SiI, MeCN, room temp., 85%; v, 2-propyllithium, Et_2O, ultrasound, room temp.; vi, *p*-TsCl, $CHCl_3$, room temp., 42% from 7



Scheme 3 *Reagents and conditions*: i, *hν* (450 W Hg lamp), pyrex, EtOAc, 87%; ii, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp., 50%; iii, O_3, CH_2Cl_2, −78 °C, 87% or $RuCl_3$, MeCN–CCl_4–H_2O, $NaIO_4$, 76%

Footnote

† Satisfactory spectral data were obtained for all compounds. *Selected spectral data*: **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.70–3.50 (1H, m), 2.20–0.70 (8H, series of m), 1.48 (3H, s), 0.87 (6H, d, J = 6.66 Hz); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 195.3, 92.1, 58.8, 43.8, 40.3, 34.4, 32.4, 24.8, 23.8, 19.9, 19.4, 19.3. **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.20–6.00 (1H, m), 5.20–4.90 (2H, m), 2.34 (2H, d, J = 5.32 Hz), 1.90–1.40 (6H, m), 1.23 (3H, s), 0.89 (6H, d, J = 5.97 Hz); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 214.0, 142.9, 112.8, 50.5, 45.2, 41.9, 36.7, 31.9, 24.3, 22.5, 19.7, 19.6; **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.89 (1H, dd, J_1 = 17.49 Hz, J_2 = 10.74 Hz), 5.85 (1H, s), 5.20–4.90 (2H, m), 2.50–2.10 (3H, m), 2.10–1.70 (2H, m), 1.19 (3H, s), 1.09 (6H, d, J = 6.9 Hz); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 202.1, 170.0, 140.9, 122.7, 114.0, 47.5, 35.4, 35.0, 25.0, 22.9, 20.8, 20.6; **8**: $[\alpha]_D^{25}$ = +112.5 from **1** and $[\alpha]_D^{25}$ = +109 from **9** (lit. $[\alpha]_D$ = +116).[7]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.37 (1H, s), 5.78 (1H, dd, J_1 = 17.24 Hz, J_2 = 10.73 Hz), 5.10–4.90 (2H, m), 2.40–2.20 (3H, m), 1.81 (3H, s), 1.73 (3H, s), 1.70–1.40 (2H, m), 1.18 (3H, s), 1.06 (3H, d, J = 6.85 Hz), 1.45 (3H, d, J = 6.01 Hz); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 149.7, 146.3, 128.1, 124.5, 119.7, 112.4, 42.2, 37.8, 29.4, 25.3, 24.7, 23.8, 23.1, 20.7, 19.7; **13**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.68 (1H, dd, J_1 = 14.8 Hz, J_2 = 2.93 Hz), 2.43 (1H, m), 2.40–2.10 (2H, m), 1.80–1.40 (4H, m), 1.38–1.10 (1H, m), 1.20 (3H, s), 0.95 (3H, d, J = 6.86 Hz), 0.88 (3H, d, 6.83 Hz); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 218.4, 70.3, 62.5, 57.8, 49.4, 36.5, 30.4, 26.2, 24.3, 19.1, 17.7, 13.7; **15**: $[\alpha]_D^{25}$ = +289.45; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60–2.00 (8H, series of m), 1.90–1.00 (1H, m), 1.24 (3H, s); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 221.4, 220.0, 57.0, 53.8, 37.9, 36.9, 30.6, 21.4, 20.6.

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