

Restructuring α -pinene: novel entry into diverse polycarbocyclic frameworks

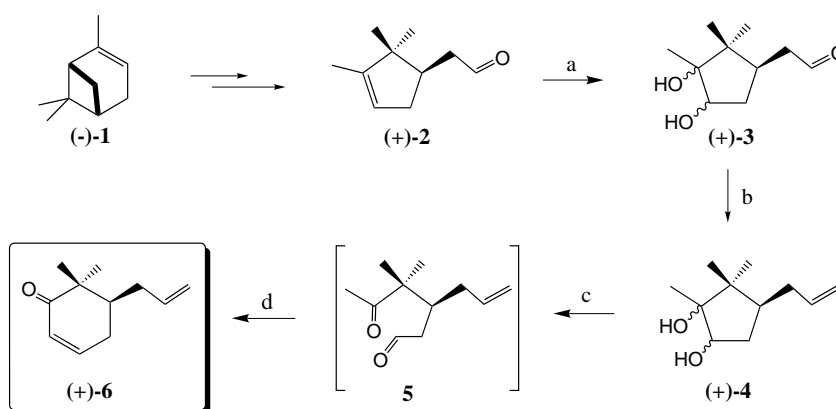
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Abstract—(–)- α -Pinene **1** has been restructured into a chiral cyclohexenone (+)-**6**, in which the functionalities were integrated to afford bicyclo[3.3.1]nonan 3,7-diones and a novel tricyclic skeleton **16** related to the sesquiterpene clovene. Intramolecular [2+2] photocycloadditions in (+)-**6** and related 5-alkenylcyclohexenones provided an entry into some novel bridged tricyclic systems.

(–)- α -Pinene **1**, a monoterpene found abundantly in Nature has been extensively explored as a chiron in diverse natural product synthesis.¹ In many such endeavours, (+)-campholenic aldehyde **2** obtained from (–)-**1** through epoxidation and Lewis acid mediated fragmentation² has proved to be a valuable synthon.³ However, the built-in chirality and functionalities in (+)-**2** offer many new possibilities for elaboration into diverse polycyclic frameworks, particularly those of relevance in natural products syntheses. Herein, we report the acquisition of several new carbocyclic frameworks from (+)-**2** through short, simple synthetic manoeuvres.

To begin with, expansion of the five-membered ring in (+)-**2** and homologation of the side arm appeared to be a useful transformation as the resultant cyclohexenone (+)-**6** would be a more versatile building-block for further elaboration. Consequently, (+)-campholenic aldehyde **2**,² was subjected to OsO₄ mediated dihydroxylation to exclusively furnish one diastereomer of the diol (+)-**3**. Wittig olefination in (+)-**3** furnished quantitatively the diol-olefin (+)-**4**. The diol moiety in (+)-**4** was cleaved with periodate and the resulting 1,5-dicarbonyl compound **5** on intramolecular aldol cyclisation in the presence of *p*TSA afforded enone (+)-**6**⁴ (Scheme 1).



Scheme 1. Reagents and conditions: (a) OsO₄, NMMO, ^tBuOH–H₂O–acetone (5:2:5), rt, 3 days, 82%; (b) PPh₃MeBr, ^tBuOK, THF, 30 min, quant.; (c) NaIO₄, CH₂Cl₂–H₂O (10:1), 6 h; (d) *p*TSA, cyclohexane, 80°C, 2 h, 68% for two steps.

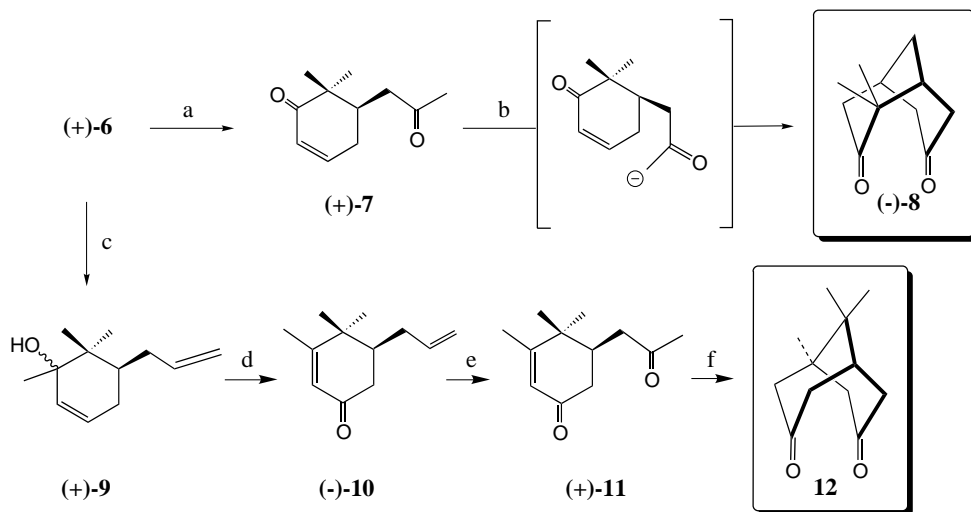
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From (+)-**6**, we set out to explore entry into the bicyclo[3.3.1]nonane system, which is present among many natural products and synthetic access to this ring system is rather limited.⁵ In our approach, we decided to synchronise the available functionalities in (+)-**6** for an intramolecular Michael cyclisation to deliver the bicyclo[3.3.1]nonane system laced with functionalities. Thus, (+)-**6** was subjected to Wacker–Tsuji oxidation⁶ to generate the methyl ketone (+)-**7** with a Michael donor site. On exposure to base, (+)-**7** successfully underwent the projected cyclisation to afford (–)-**8**⁴ in enantiomerically pure form in 76% yield in a short sequence from (+)-**2** (Scheme 2).

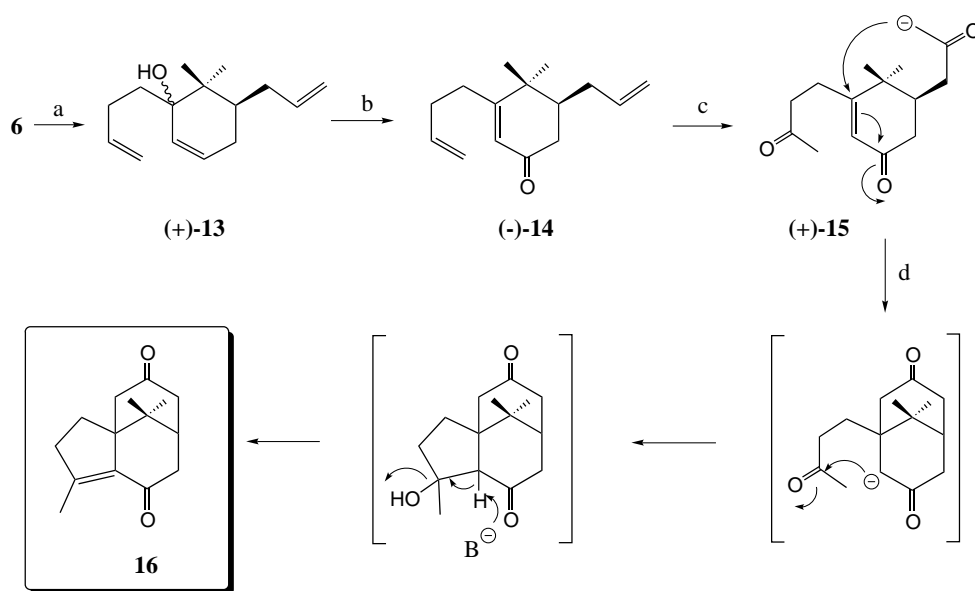
Another variant of the intramolecular Michael addition from (+)-**6** to deliver the bicyclo[3.3.1]nonane-3,7-

diones with additional substituents was explored. Addition of methyl lithium to (+)-**6** yielded the tertiary allylic alcohol (+)-**9** in good yield. Oxidation of (+)-**9** with PCC led to the transposed enone (–)-**10**. Wacker–Tsuji oxidation⁶ in (–)-**10** afforded the enone (+)-**11**. The Michael acceptor centre in this substrate is sterically quite hindered due to the presence of the *gem*-dimethyl group, but on exposure to base it underwent smooth intramolecular Michael addition to yield **12**⁴ as the exclusive product in 80% yield. The presence of symmetry in **12** revealed through its ¹H and ¹³C NMR (8 resonances for 12 carbons) spectra facilitated its characterisation (Scheme 2).

Our next objective was to elaborate the above-mentioned strategy to some more complex natural product



Scheme 2. Reagents and conditions: (a) PdCl₂, CuCl, O₂, DMF–H₂O (3:1), rt, 2 h, 90%; (b) ^tBuOK, THF–^tBuOH (1:1), 1 h, 76%; (c) MeLi, THF, 10°C, 1 h, 90%; (d) PCC, CH₂Cl₂, 6 h, 95%; (e) PdCl₂, CuCl, O₂, DMF–H₂O (3:1), rt, 2 h, 92%; (f) ^tBuOK, THF–^tBuOH (1:1), 1 h, 80%.



Scheme 3. Reagents and conditions: (a) *n*-butenyl bromide, Li, THF, sonication, 20°C, 75%; (b) PCC, CH₂Cl₂, 6 h, 93%; (c) PdCl₂, CuCl, O₂, DMF–H₂O (3:1), rt, 2 h, 86%; (d) ^tBuOK, THF–^tBuOH (1:1), 1 h, 54%.

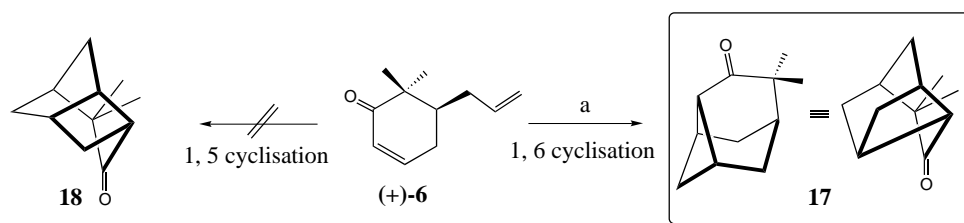
carbocyclic skeleta possessing the bicyclo[3.3.1]nonane motif. Towards this end, (+)-**6** was subjected to Barbier reaction with butenyl bromide to afford (+)-**13** (Scheme 3). PCC oxidation of (+)-**13** readily furnished the transposed enone (–)-**14**. The two terminal olefin bearing side arms of (–)-**14** were subjected to double Wacker–Tsuji oxidation⁶ to afford the diketo-enone (+)-**15**. The plan was to affect tandem Michael addition–aldol cyclisation in a one-pot reaction in (+)-**15** to furnish a tricyclic system directly. In the event, on exposure to base (+)-**15** yielded exclusively the anticipated, doubly cyclised product **16**.⁴ The tricyclic C₁₅-keto-enone **16** is an unnatural sesquiterpenoid having the carbocyclic skeleton present in the sesquiterpene clovene⁷ except that the disposition of the methyl groups on the carbocyclic framework is different (Scheme 3).

At this stage, attention was turned towards the photochemical reactions of the α -pinene derived cyclohexenones described above as they offered some interesting possibilities. The intramolecular [2+2] photocycloadditions between enone and olefin moieties have been extensively studied in 2-, 3- and 4- substituted alkenyl cyclohexenones and found numerous applications in synthesis.⁸ However, photochemistry of 5-alkenyl cyclohexenones has been sparsely investigated possibly due to their difficult accessibility. Hence, the readily available 5-allyl cyclohexanones (+)-**6** and (–)-**14** attracted our attention and their response to photoirradiation was investigated. When cyclohexenone (+)-**6** was irradiated with a 125W UV lamp, a single tricyclic product **17**⁴ was obtained in 70% yield. The ¹³C NMR spectrum of **17** had 8 lines indicating symmetry. The presence of a plane of symmetry in the 1,6 addition product (which is absent in the 1,5 addition product **18**) led to the structure **17**. This mode of addition observed here is against the ‘rule of five’ for intramolecular [2+2] photocycloadditions⁹ and points to the fact that no

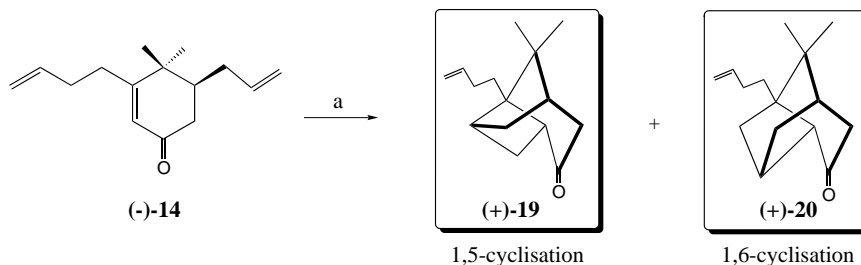
strict generalisation can be made for such reactions.¹⁰ The 1,6 intramolecular photoaddition is perhaps sterically more favourable in this case than its 1,5 counterpart leading to such selectivity (Scheme 4).

The 5-alkenyl cyclohexenone (–)-**14** has an additional reaction centre in the form of a butenyl moiety, and therefore the interest in its photoreactivity was two-fold. First was to explore if any regioselectivity could be observed between the two terminal double bonds during the [2+2]-cycloaddition, and second, whether the ‘rule of five’ holds true in this case or not. On irradiation, (–)-**14** gave rise to a mixture of products from which two major tricyclic products (+)-**19**⁴ (45%) and (+)-**20**⁴ (15%) were separated and characterised. The structural assignments to (+)-**19** and (+)-**20** were secured on the basis of ¹H–¹H COSY data for both of these compounds. In (+)-**19** and (+)-**20** the allyl arm had added on to the enone double bond, leaving the butenyl part intact. The major product (+)-**19** (45%) originated through [2+2]-cycloaddition according to the ‘rule of five’, whereas the relatively less abundant product (+)-**20** (15%) was a consequence of 1,6 addition (Scheme 5).

In summary, we have restructured the monoterpene α -pinene (–)-**1** to a six-membered enone (+)-**6** embellished with functionalities as well as chirality via the intermediacy of α -campholenic aldehyde (+)-**2**. Enone (+)-**6** was utilised to construct the bicyclo[3.3.1]nonane framework and the methodology has been extended towards the rapid construction of the tricyclic skeleton present in the sesquiterpene clovene employing intramolecular, Michael addition and aldol cyclisation in tandem. Photochemistry of 5-alkenyl cyclohexenones (+)-**6** and (–)-**14** has provided a facile entry to several new tricyclic skeleta in chiral form through intramolecular [2+2]-cycloadditions.



Scheme 4. Reagents and conditions: (a) *hν* (125 W Hg vap. lamp, Pyrex filter), C₆H₆, 3 h, (70%).



Scheme 5. Reagents and conditions: (a) *hν* (125 W Hg vap. lamp, Pyrex filter), C₆H₆, 3 h, (+)-**19** (45%), (+)-**20** (15%).

Acknowledgements

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4. All new compounds reported here were duly characterised on the basis of spectral (IR, ^1H (2D wherever required) and ^{13}C NMR) and LRMS data. Selected spectral data: **6**: $[\alpha]_{\text{D}}^{25}$: +19.0 ($c=1.0$, CHCl_3); IR (neat): 1676 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.86–6.80 (1H, m), 5.96 (1H, d, $J=9$ Hz), 5.80–5.66 (1H, m), 5.08–5.03 (2H, m), 2.51–2.31 (2H, m), 2.15–2.06 (1H, m), 1.97–1.83 (2H, m), 1.19 (3H, s), 1.01 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 204.6, 147.4, 136.9, 128.1, 116.6, 45.3, 43.2, 34.0, 28.4, 22.5, 19.0; Mass (E.I., 70 eV): m/z 165 (M^+ +1). **8**: $[\alpha]_{\text{D}}^{25}$: -80.7 ($c=1.76$, CHCl_3); mp: 86–88°C; IR (thin film): 1701 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.89–2.81 (2H, m), 2.71–2.52 (3H, series of m), 2.46–2.24 (4H, series of m), 2.09–2.02 (1H, m), 1.28 (3H, s), 1.09 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 213.5, 208.1, 48.5, 48.1, 45.1, 44.35, 44.32, 33.7, 29.2, 27.7, 22.4; Mass (E.I., 70 eV): m/z 180 (M^+). **12**: mp: 244–246°C; IR (thin film): 1711 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.81 (2H, dd, $J=16.2$, 6.3 Hz), 2.55 (2H, d, $J=16.2$ Hz), 2.30–2.10 (3H, m), 2.13 (2H, d, $J=16.2$ Hz), 1.32 (6H, s), 1.00 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 208.8 (2×C), 51.9 (2×C), 45.3 (2×C), 43.6, 41.2, 35.4, 24.3, 22.8 (2×C); Mass (E.I., 70 eV): m/z 194 (M^+). **16**: mp: 90–92°C; IR (thin film): 1710, 1673, 1612 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.89 (1H, dd, $J=14.1$, 6.2 Hz), 2.78–2.64 (2H, series of m), 2.56–2.46 (1H, m), 2.33–2.20 (5H, m), 2.10 (3H, s), 2.06–1.96 (1H, m), 1.54–1.48 (1H, m), 1.31 (3H, s), 1.10 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 209.6, 197.3, 155.7, 136.2, 57.4, 49.7, 46.2, 44.3, 43.5, 36.5, 35.6, 31.5, 24.2, 22.7, 16.6; Mass (E.I., 70 eV): m/z 233 (M^+ +1). **17**: IR (neat): 1709, cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.69 (1H, t, $J=5.1$ Hz), 2.57 (2H, q, $J=5.4$ Hz), 2.42–2.35 (1H, m), 2.20–2.14 (2H, m), 1.97 (1H, br. s), 1.82 (2H, dd, $J=13.7$, 4.0 Hz), 1.33 (1H, d, $J=8.7$ Hz), 1.12 (6H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 219.1, 47.0, 44.9, 40.2, 40.0, 35.6 (2×C), 30.2 (2×C), 23.4 (2×C); Mass (E.I., 70 eV): m/z 164 (M^+ +1). **19**: $[\alpha]_{\text{D}}^{25}$: +45.4 ($c=1.08$, CHCl_3); IR (neat): 1702, 1641 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 5.88–5.82 (1H, m), 5.01 (1H, dd, $J=17.0$, 1.5 Hz), 4.97 (1H, d, $J=10.0$ Hz), 2.69–2.63 (2H, m), 2.51–2.40 (4H, m), 2.30–2.20 (1H, m), 2.19–2.09 (1H, m), 2.03 (1H, t, $J=6.0$ Hz), 1.63–1.54 (2H, m), 1.51 (1H, d, $J=13.0$ Hz), 1.39 (1H, d, $J=11.5$ Hz), 0.87 (3H, s), 0.84 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 215.8, 139.0, 114.5, 54.8, 50.5, 46.5, 45.1, 43.3, 39.6, 38.9, 31.1, 29.7, 27.1, 23.3, 18.5. **20**: $[\alpha]_{\text{D}}^{25}$: +9.6 ($c=0.52$, CHCl_3); IR (neat): 1707, 1641 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 5.84–5.76 (1H, m), 5.03 (1H, dd, $J=17.0$, 1.5 Hz), 4.96 (1H, d, $J=10.0$ Hz), 2.63–2.59 (1H, m), 2.55 (1H, d, $J=5.5$ Hz), 2.48 (1H, q, $J=6.0$ Hz), 2.27–2.23 (1H, m), 2.05–2.02 (2H, m), 1.98–1.93 (3H, series of m), 1.73–1.69 (2H, m), 1.56–1.50 (1H, m), 1.37–1.31 (1H, m), 1.13 (3H, s), 0.89 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 215.1, 138.8, 114.4, 54.0, 53.4, 43.8, 40.7, 37.6, 34.9, 33.8, 32.7, 30.9, 29.7, 24.6, 23.7.
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