Cycloaddition between electron deficient partners: an efficient regio- and stereoselective synthesis of functionalised bicyclo[2.2.2]octenones. A tandem alkylation, stereochemical inversion and aldol condensation

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Abstract—A novel one step regio- and stereoselective synthesis of functionalised bicyclo[2.2.2]octenones from readily available aromatic precursors is described. The methodology involved in situ generation of reactive spiroepoxycyclohexadienones and \( \pi^+ + \pi^+ \) cycloaddition with methyl vinyl ketone. Study on \( \pi \)-facial alkylation that led to the formation of homobrendane derivatives as a result of stereochemical inversion and aldol condensation in tandem, is also presented. The crystal structure of 6-acetyl-1-methoxy-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,20]oxirane and 3-methoxy-4,6,9-trimethyltricyclo[4.3.1.0\textsuperscript{3,7}]decan-8-en-5-one-spiro[2,20]oxirane is also reported.

1. Introduction

Bridged bicyclo[2.2.2]octenones of type 1 are unique molecular systems since they offer a broad range of chemical reactivity by virtue of the rigid molecular framework, interactions among functional groups such as homoconjugation and electronic control and hence they have served as precursors for stereoselective synthesis of diverse molecular frameworks.\(^1\text{-}^3\) While simple bicyclo[2.2.2]octenones are prepared in several steps via Diels–Alder reaction of cyclic 1,3-dienes and ketene equivalents followed by manipulation of the resulting adduct,\(^5\) double Michael addition,\(^5\text{a,c}\) Michael addition followed by reductive amination,\(^5\text{b}\) homoallyl–homoallyl radical rearrangement\(^6\) and cycloaddition of \( \alpha \)-quinoneketals and related species\(^7\) have been employed for the synthesis of complex bicyclo[2.2.2]octenones. However, these methods have several limitations with regard to introduction of functional groups and substituents on the bicyclo[2.2.2]octane frame and often give a mixture of regio-isomers. In view of the recent interest in the design of new methods that generate complex structures with atom economy and stereoselectivity,\(^5\text{a,b}\) we developed a method for generation of molecular complexity from simple aromatic precursors that involved cycloaddition of spiroepoxycyclohexa-2,4-dienones with electron rich \( \pi \)-partners\(^{10\text{a,b}}\) and also reported the reaction of cyclohexadienones even with electron deficient \( \pi \) partners such as acrylates.\(^{10\text{c}}\)

Keywords: Spiroepoxycyclohexa-2,4-dienones; Cycloaddition; Bicyclo[2.2.2]octenones.

2. Results and discussion

Towards the synthesis of 2, we attempted in situ generation of the spiroepoxycyclohexadienone by the periodate oxidation\(^1\text{I}\) of hydroxymethyl phenols and interception with methyl vinyl ketone. Thus, a solution of \( \alpha \)-vanillyl alcohol and methyl vinyl ketone in acetonitrile was treated with aqueous sodium metaperiodate at \( \sim 5 \) °C, following a procedure developed in our laboratory.\(^{11\text{c}}\) This gave the
adduct 7 in excellent yield (Scheme 1). The gross structure of the adduct was easily revealed from the following spectroscopic data. The IR spectrum showed absorption bands at 1745 and 1712 cm$^{-1}$, which suggested the presence of two carbonyl groups. The $^1$HNMR (300 MHz) spectrum of the adduct exhibited characteristic signals at $\delta$ 6.56 (superimposed dd, $J_1 = J_2 = 8.5$ Hz, 1H) and 6.25 (d, $J$, 8.5 Hz, 1H) for the $\gamma$- and $\beta$- protons of $\beta,\gamma$-alkene moiety. It also showed a signal at $\delta$ 3.55 (s, 3H) due to –OMe and a highly characteristic AB pattern due to the methylene protons of an oxirane ring which appeared separately at $\delta$ 3.12 (part of AB system, $J_{AB} = 6.3$ Hz, 1H) and 2.83 (part of AB system, $J_{AB} = 6.3$ Hz, 1H). In addition, signals were observed at $\delta$ 3.27 (m, 1H), 2.59 (m, 1H), 2.25 (s overlapped with another signal, 4H, COCH$_3$+H), 1.95 (m of d, $J$=15 Hz, 1H). The $^{13}$C NMR spectrum also gave characteristic signals at $\delta$ 206.4 and 201.8 for the two carbonyl groups. The olefinic carbons were observed at $\delta$ 133.2 and 126.8. Other signals were observed at $\delta$ 87.03, 57.2, 54.5, 53.1, 49.3, 38.1, 32.7 and 27.3 for methine, methylene and quaternary carbons. These spectral features suggested the structure of the adduct but it was difficult to ascertain the stereochemical orientation of the oxirane ring, and distinguish between 7 and its regio-isomer 8 on the basis of spectral data alone. Hence, a single crystal structure determination was undertaken which confirmed structure 7 for the adduct (Fig. 2).

In order to generalize the aforementioned cycloaddition, oxidation of various hydroxymethyl phenols to the corresponding spirooxypocyclohexa-2,4-dienones and their interception with methyl vinyl ketone were examined (Scheme 2). All the hydroxymethyl phenols 9a–e gave the corresponding adducts 11a–e in moderate to excellent yields. The substituents on the aromatic ring (and hence in cyclohexa-2,4-dienones 10a–e) appear to govern the efficiency of cycloaddition in a subtle manner. The methyl groups at C 2 and/or C 4 of the cyclohexadienones such as 10c, 10d enhance the efficiency of cycloaddition. Similarly, the presence of a methoxy group at C 2 (as in 6) led to an excellent yield of the adduct but the cycloaddition of 10e having a methoxy group at C 2 and allyl moiety at C 4 proceeds with moderate efficiency. Interestingly, the spirooxypocyclohexadienone 10b containing bromine at C 4 also underwent cycloaddition with reasonable efficiency to furnish the corresponding adduct. The structures of all adducts were deduced from their spectroscopic and analytical data, and comparison of their spectral features with those of 7.

It may be mentioned that electron deficient systems such as cyclohexa-2,4-dienones and $\pi$-benzoquinone ketals generally react with electron rich $\pi$ partners in inverse electron demand fashion. Further, it is interesting to note the regio-selectivity in the above cycloaddition wherein the $\alpha$-carbon of methyl vinyl ketone is bonded to C 2 of cyclohexa-2,4-dienones. Similar regioselectivity is also observed during cycloaddition of cyclohexa-2,4-dienones.

![Scheme 1](image1.png)

![Scheme 2](image2.png)

![Figure 1](image3.png)

![Figure 2](image4.png)
even with electron rich dienophiles such as vinyl ethers wherein the carbon having polar electron donating group forms bond with C₂ carbon of cyclohexa-2,4-diene.₁²,₁³

After having an efficient access to bicyclo[2.2.2]octenones, we explored the alkylative stereochemical inversion of acetyl group in 11c. We considered it possible to selectively alkylate the methine carbon α to the carbonyl group of acetyl group. Further, it was thought that the electrophile might approach in a stereoselective manner from the endo face since the enolates derived from simple bicyclo[2.2.2]-octenones are known to undergo stereoselective alkylation from the π-face.₁⁴

Thus, the epoxyketone 11c was treated with sodium hydride and methyl iodide at 80 °C. However, a very complex mixture of products was obtained. After considerable experimentation, it was observed that the treatment of 11c with sodium hydride and methyl iodide at ~0 °C led to a reasonably clean reaction from which five closely related products 12–14 were isolated (Scheme 3). The structures of all the compounds were deduced from their spectroscopic data. Though the gross structure of the compound 13a was easily deduced from the spectroscopic data, the orientation of the methyl group present in the cyclopentanone ring was not easily discernible. Hence, X-ray single crystal structure determination of 13a was undertaken which confirmed its formulation (Fig. 3).

The formation of 12, 13 and 14 clearly indicated that the alkylation of 11c had indeed occurred stereoselectively from the endo face so as to push the acetyl group to theexo orientation, as desired. However, multiple alkylation and aldol condensation also occurred to give the homobrendane derivatives 12–14. Though the aforementioned reaction may not appear synthetically useful in this particular case, it provides an interesting class of compound not readily accessible otherwise, and importantly this observation suggests the possibility of generating stereochemical diversity from suitably designed endo Diels–Alder adducts.

3. Conclusion

In summary, a new one step method leading to complex bicyclo[2.2.2]octenones having an endo acetyl moiety, is described. The observations on alkylative stereochemical inversion provide further insight into the chemistry of such highly functionalised bicyclo[2.2.2]octenones and pave the way for the strategic design and synthesis of molecular systems that are not readily accessible otherwise.

4. Experimental

4.1. General

IR spectra were recorded on Nicolet Impact 400 FT-IR Instrument. UV spectra were recorded on Shimadzu UV 160 or Shimadzu U 260 instrument. ¹H NMR and ¹³C NMR were recorded on Bruker Avance-400 NMR spectrometer, Varian NMR and Varian VXR 300 instruments. Micro-analyses were done on a CEST 1106 instrument and HRMS on a Q-Tof micro (YA-105) Mass Spectrometer. Melting points were determined on a Veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous sodium sulphate. Reactions were monitored with thin layer chromatography silica gel and spots were visualized with iodine vapor. Column chromatography was performed using Acme/SRL silica gel (60–120 or 100–200 mesh). The elution was done with petroleum ether (60–80 °C) and ethyl acetate mixtures. The fractions eluted from column were concentrated at reduced pressure on a Buchi-RE 111 rotary evaporator.

4.1.1. 6-Acetyl-1-methoxy-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2]oxiran (7). To a solution of o-vanillyl alcohol (2 g, 12.98 mmol) in acetonitrile (50 mL) was added methyl vinyl ketone (5.4 mL, 64.94 mmol) and the reaction mixture was cooled in an ice bath (0–5 °C). A solution of NaIO₄ (5.6 g, 25.97 mmol) in water (50 mL) was then added dropwise to the reaction mixture over 30 min with stirring. After stirring for 1 h, it was brought to ambient temperature (~28 °C) and further stirred for 6 h. The reaction mixture was filtered and organic layer was separated and the
aqueous layer was extracted with ethyl acetate (3×50 mL). The organic extracts were combined, washed with brine (50 mL) and dried over anhydrous sodium sulfate. Removal of solvent under vacuum gave a residue, which was chromatographed on silica gel. Elution with petrol-ether (60–80 °C)–ethyl acetate (84:16) gave the adduct 7 (1.9 g, 69%) as a colorless solid, mp 101–103 °C. IR (film) νmax: 1712, 1745 cm⁻¹. ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 6.56 (superimposed dd, J₁g=J₁e=8.5 Hz, 1H, γ- proton of the β,γ-enone moiety), 6.25 (d, J=8.5 Hz, 1H, β-H of β,γ-enone moiety), 3.55 (s, 3H, –OMe), 3.12 (part of an AB system, JAB=6.3 Hz, 1H, CH₂– of oxirane ring), 2.83 (part of an AB system, JAB=6.3 Hz, 1H, CH₂– of oxirane ring), 2.37 (m, 1H), 2.59 (m, 1H), 2.25 (m overlapped with another signal, 4H, COCH₂+1H), 1.95 (m of d, J=15 Hz, 1H), 1.344 Mg/m³, 0.40 ppm 1H, OCH 2), 2.83 (part of an AB system, JAB=6.3 Hz, 1H, CH₂– of oxirane ring), 2.37 (m, 1H), 2.59 (m, 1H), 2.25 (m overlapped with another signal, 4H, COCH₂+1H), 1.95 (m of d, J=15 Hz, 1H), 1.344 Mg/m³, 0.40 ppm

Crystal data. C₇H₇O₃. M=222.23, monoclinic, P2₁/a, Z=4, λ=0.70930 Å, a=8.66300(18) Å, b=12.47700(17) Å, c=10.49200(18) Å, V=1098.1(3) Å³, T=293(2) K, Dₐ=1.344 Mg/m³, µ=0.101 mm⁻¹, F(000)=472, size=0.4×0.4×0.25 mm³. Reflections collected/unique=1736/1736 [R(int)=0.0000], final R indices [I>2σ(I)]: R₁=0.0413, wR₂=0.1056, R indices (all data): R₁=0.0495, wR₂=0.1121.

CCDC 231385.

4.1.4. 6-Acetyl-8-methyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2']oxirane (11c). A solution of 5-methylsalicyl alcohol 10c (2 g, 14.5 mmol) and methyl vinyl ketone (6 mL, 72.46 mmol) in acetonitrile (50 mL) was cooled in an ice bath (0–5 °C) and a solution of NaIO₄ (6.2 g, 28.9 mmol) in water (60 mL) was added dropwise to the reaction mixture over 45 min with stirring. After stirring for 1 h, it was brought to ambient temperature (~28 °C) and further stirred for 6 h. Work-up as described above followed by removal of solvent gave a residue which after column chromatography (pet-ether–ethyl acetate (82:18) furnished the adduct 11c (1.3 g, 44%) as a solid, mp 96–98 °C. IR (film) νmax: 1739, 1712 cm⁻¹. ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 5.73 (d, J=5.7 Hz, 1H), 3.53 (d, J=5.7 Hz, 1H), 3.14 (m merged with another signal, 1H, CH₂– of an AB system, JAB=6 Hz, total 2H), 2.85 (part of an AB system, JAB=6 Hz, 1H, OCH₂), 2.35 (br s, 1H), 2.19 (s merged with a m, total 4H), 2.03–1.98 (m, 1H), 1.91 (s, 3H). ¹³C NMR (75 MHz, CDCl₃+CDCl₄): δ 204.39, 203.17, 145.1, 118.73, 57.24, 52.13, 49.68, 48.25, 43.74, 28.34, 23.57, 20.69. Analysis: Found, C, 69.53; H, 7.29% requires C, 69.9, H, 6.8% for C₁₁H₁₄O₃. Mass (m/z): 206 (M+)..

4.1.5. 6-Acetyl-1,8-dimethyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3,2']oxirane (11d). To a solution of 3,5-dimethyl salicyl alcohol 10d (2 g, 13.16 mmol) and methyl vinyl ketone (5.3 mL, 65.79 mmol) in acetonitrile (50 mL) was added a solution of NaIO₄ (5.7 g, 26.31 mmol) in water (60 mL) dropwise at 0–5 °C. After stirring for 1 h the reaction mixture was brought to ambient temperature (~28 °C) and further stirred for 4 h. Work-up as described above followed by removal of solvent gave a residue which was chromatographed on silica gel. Elution with petrol–ether–ethyl acetate (86:14) furnished the adduct (2.28 g, 78.65%) as a solid, mp 65–66 °C. IR (film) νmax: 1736/1736 cm⁻¹. ¹H NMR (300 MHz, CDCl₃+CDCl₄): δ 5.51 (s, 1H), 3.11 (part of an AB system, JAB=6 Hz, 1H), 2.97–2.95 (m, 1H), 2.85
(part of an AB system, $J_{AB}=6$ Hz, 1H, OCH$_2$), 2.42–2.35 (m, 2H), 2.15 (s, 3H), 1.93 (s, 3H), 1.71–1.70 (m, 1H), 1.26 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 206.43, 203.52, 142.73, 124.98, 56.96, 52.16, 51.45, 51.04, 43.81, 31.43, 28.11, 20.53, 15.54. Analysis: Found: C, 70.56%; H, 6.90% requires C, 70.90, H, 7.20 for C$_{13}$H$_{24}$O$_3$. Mass (m/z): 220 (M$^+$).

4.1.6. 6-Acetyl-8-allyl-1methoxy-bicyclo[2.2.2]oct-7-en-2-one-spiro[3.2]oxirane (11e). To a solution of 5-allyl-3-methoxy salicylic alcohol 10e (2 g, 10.31 mmol) and methyl vinyl ketone (4.3 mL, 51.54 mmol) in acetonitrile (50 mL) was added a solution of NaIO$_4$ (4.4 g, 20.6 mmol) in water (45 mL) dropwise at 0–5 °C. After stirring for 1 h, the reaction mixture was brought to ambient temperature (~28 °C) and further stirred for 6 h. Work-up as described above followed by removal of solvent under vacuum gave a residue which was chromatographed on silica gel. Elution with pet-ether (60–80 °C)–ethyl acetate (90:10) gave the adduct 11e as a colourless liquid (1.1 g, 40%). IR (film) $\nu$max: 1745, 1710 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 5.90 (br m, 1H), 5.84–5.70 (m, 1H), 5.21–5.15 (m, 2H), 3.54 (s, 3H), 3.28 (dd, $J_{1,2}=10$ Hz, $J_{2,3}=6$ Hz, 1H), 3.14 (part of an AB system, $J_{AB}=6$ Hz, 1H, OCH$_3$), 3.02 (m, 2H), 2.88 (part of an AB system, $J_{AB}=6$ Hz, 1H, OCH$_2$), 2.44 (m, 1H), 2.26 (s, 3H), 2.24–1.46 (m, 1H), 1.2 (dd of d, $J_{1,2}=12$ Hz, $J_{2,3}=6$ Hz, $J_{3,4}=2$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 206.54, 202.17, 145.15, 133.72, 119.08, 118.39, 87.18, 57.36, 54.46, 52.61, 50.20, 41.76, 39.30, 32.77, 26.89. Mass (m/z): 262 (M$^+$); ES-MS: m/z calculated for C$_{14}$H$_{18}$O$_3$: 263.1283. [M+H$^+$]; found 263.1292.

4.1.7. Alkylation of 6-acetyl-8-methyl-bicyclo[2.2.2]oct-7-en-2-one-spiro[3.2]oxirane (11c): formation of 12–14. Sodium hydride [0.166–0.2 g (60%/w/w), 2.91 mmol] was taken in a two necked flask fitted with a nitrogen inlet. It was washed with dry petroleum ether (3×5 mL) and dry THF (3 mL) was added. A solution of the compound 11c (0.4 g, 1.94 mmol) in dry THF (10 mL) and MeI (2 mL) in dry THF (4 mL) was added to sodium hydride–THF at 0 °C. After completion of reaction ( TLC, 3 h), the reaction mixture was poured into NH$_4$Cl solution, and diluted with ether. The organic layer was separated and the aqueous layer was extracted with ether (30 mL×4). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and solvent was removed under vacuum to give a residue, which was chromatographed on silica gel. Elution with pet-ether (60–80 °C)–ethyl acetate (92:8) gave a mixture of 13a and 14, which were separated by fractional recrystallization to give 13a (0.050 g, 11%) and 14 (0.090 g, 18.9%) as colourless solids. Further elution with petroleum ether (60–80 °C)–ethyl acetate (89:11) gave compound 12a (0.054 g, 12.7%) as a solid. Elution with pet-ether (60–80 °C)–ethyl acetate (82:18) gave compound 13b (0.075 g, 17.6%) as a colourless solid. Elution with pet-ether (60–80 °C)–ethyl acetate (78:22) gave the compound 12b (0.040 g, 10%) as a colourless solid.

Data for 12a. Colourless solid, mp 95 °C. IR (film) $\nu$max: 1730 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 5.82 (m of d, $J_{6,7}=4.8$ Hz, 1H), 3.06 (d, $J_{5,6}=5$ Hz, 1H), 2.66 (m, 2H), 1.92–1.83 (s overlapped with a m, total 5H), 1.58 (s, 1H), 1.06–1.35 (d overlapped with m, $J_{7,8}=7$ Hz, total 4H), 0.98 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$+CCL$_4$): $\delta$ 219.83, 144.75, 119.84, 76.57, 68.81, 52.10, 51.78, 51.54, 46.86, 45.86, 35.73, 21.24, 20.74, 11.46. Mass (m/z): 234 (M$^+$); ES-MS: m/z calculated for C$_{14}$H$_{18}$O$_3$: 235.1334. [M+H$^+$]; found 235.1377.

Data for 14. Colourless solid, mp 152 °C. IR (film) $\nu$max: 1732 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$+CCL$_4$): $\delta$ 5.79 (m of d, $J_{5,6}=4.8$ Hz, 1H), 3.13 (s, 3H), 2.77 (d, $J_{6,7}=6$ Hz, 1H), 2.65 (part of an AB system, $J_{AB}=6$ Hz, 1H), 2.43 (part of an
AB system, $J_{AB}=6$ Hz, (1H), 2.0 (m of d, $J=10.8$ Hz, 1H), 1.88 (s, 3H), 1.74 (m, 1H), 1.25–1.20 (s, 3H), 1.08–1.01 (s overlapped with a m, total 7H). $^{13}$C NMR (75 MHz, CDCl$_3$+CCl$_4$): $\delta$, 221.56, 141.96, 121.15, 81.26, 63.81, 54.86, 53.74, 51.26, 48.79, 47.74, 46.27, 36.19, 24.25, 21.25, 20.33, 20.07. Mass ($m/z$): 262 (M$^+$); ES-MS: $m/z$ calculated for C$_{16}$H$_{23}$O$_3$: 263.1647, [M+H]$^+$; found 263.1692.

Acknowledgements

We thank CSIR New Delhi for continued financial support. One of us (G.D.P.) is grateful to CSIR for a research fellowship. Thanks are also due to DST for creating a National Single Crystal X-ray diffraction facility.

References and notes


