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Studies on the synthetic utility of [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines: efficient synthesis of fused ring cyclooctanoids

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Dedicated with respect to Professor M. V. George on the occasion of his 78th birthday

Abstract—A study on the synthetic utility of [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines is described. 5–8 Fused oxa-bridged cyclooctanoids, the products of the above methodology undergo facile Diels–Alder reaction, dipolar cycloaddition, Luche reduction and selective hydrogenation over Pd/C leading to functionalized molecules, which can be transformed to oxa-bridged fused cyclooctanoids. We have shown that the carbon framework of the molecules can be directly expanded from the product, thus enhancing the synthetic versatility of the products.

1. Introduction

Strategies towards the synthesis of fused ring heterocycles and carbocycles are important as they are found in structurally complex natural products possessing potent and selective biological activities. Moreover, functionalized heterocycles are well utilized in the development and practise of modern medicinal chemistry. Though significant achievements have been made in the synthesis of medium sized heterocycles, designing efficient, short routes for the stereoselective construction of cyclooctanoids is an interesting challenge in synthetic organic chemistry.[1,2] The discovery of new, complex and architecturally interesting cyclooctane bearing frameworks from nature, particularly from microbial and other exotic sources sustains unabated interest in cyclooctanoid synthesis.[1] Some bioactive cyclooctanoids are shown in Figure 1.

Eight-membered rings are notoriously difficult to prepare because of the unfavourable entropic and enthalpic effects, as well as the propensity for transannular interactions.[3] Fragmentation of complex bicyclic systems,[4a–d] metal-mediated synthesis[4e] and acyclic ring closures[4f] are the commonly used methods. [3,3] Sigmatropic rearrangements[4g,h] of smaller rings to such skeletons and transition metal-mediated cycloadditions[5] provide another interesting route to cyclooctanoids. Among the various methods for the synthesis of eight-membered rings,[6] higher-order cycloadditions[7] are important because of their ability to produce complex molecules with extensive functionality in a single step with good control over the creation of new stereocentres. Many of the strategies towards cyclooctanoids have been developed in the context of a specific target, but their generality, operational simplicity and regio-and stereocontrol element still remain to be fully delineated.

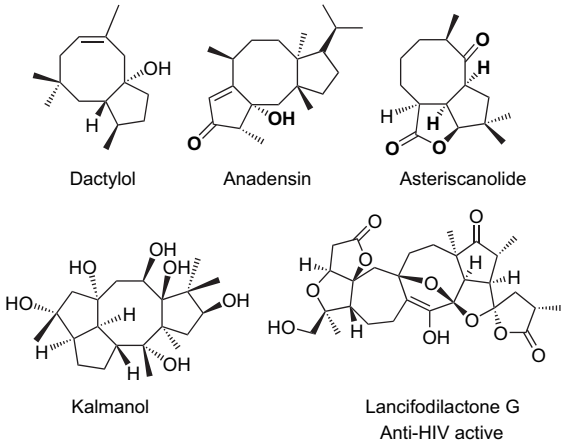

Figure 1. Some of the biologically active cyclooctanoids.

Keywords: [6+3] Cycloaddition; Diels–Alder reaction; Luche reduction; Hydrogenation; Oxa-bridged fused cyclooctanoids.
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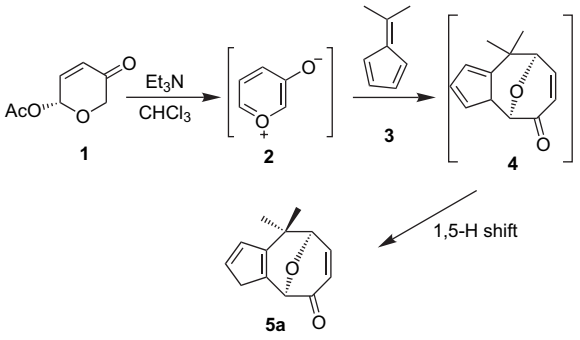
We have recently reported a facile [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines leading to the formation of 5–8 fused oxa-bridged cyclooctanoids (Scheme 1).[8] The [6+3] adducts obtained by the present methodology contain an α,β-unsaturated ketone, an oxa-bridge and a cyclopentadiene functionality, which make these adducts potentially amenable to a number of synthetic transformations. In addition, depending on the type of fulvene and 3-oxidopyrylium betaine used, manipulations can also be carried out in the eight-membered ring. We have carried out synthetic transformations of the adduct obtained by the above methodology with an aim to show the synthetic utility of the reaction and our results are described in this communication.



Scheme 1.

2. Results and discussion

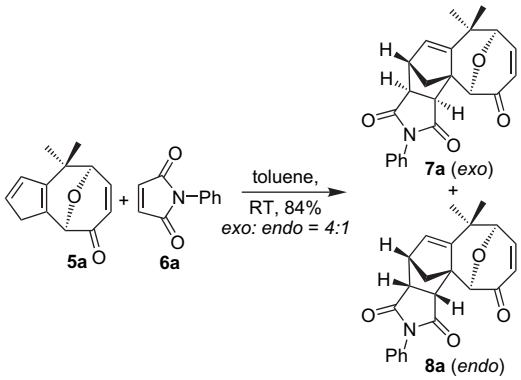
Our investigations involved the synthetic transformations of the [6+3] adduct **5a** in order to check the feasibility of the novel methodology. We have carried out transformations at three points in the molecule viz the cyclopentadiene part, α,β-unsaturated ketone functionality and at the stereocentre in the eight-membered ring corresponding to the C-6 substituent in the fulvene.

2.1. Synthetic transformations in the cyclopentadiene part

The cyclopentadiene part of **5a** can undergo cycloaddition reactions with a variety of partners and the adducts obtained can be synthetically manipulated as per our target. Keeping this aim in mind, at first we carried out the Diels–Alder cycloaddition reactions of the adduct with some selected dienophiles. The reaction of [6+3] adduct **5a** with *N*-phenyl maleimide **6a** in toluene at rt proceeded smoothly affording a 4:1 mixture of *exo* and *endo* adducts **7a** and **8a**, respectively, in 84% yield (Scheme 2).

The structure assigned to the products **7a** and **8a** was supported by spectral analysis. Finally the structure of the adducts was unambiguously proved by the single crystal X-ray analysis of *exo* adduct **7a** (Fig. 2).[9]

Similar reactivity was observed with other selected dienophiles and the results are summarized in Table 1. These results show that the 5–8 fused cyclooctanoid having the cyclopentadiene moiety can undergo facile [4+2]



Scheme 2.

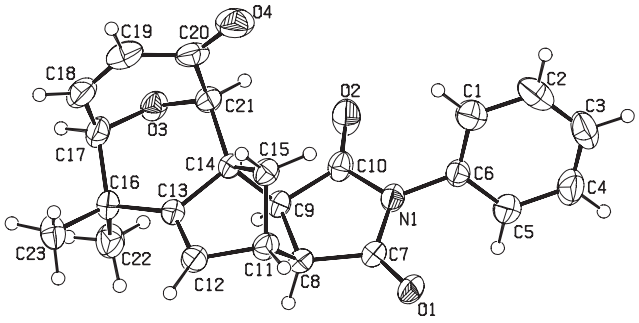
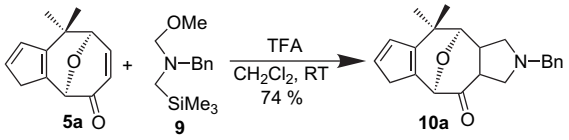


Figure 2. ORTEP plot for X-ray crystal structure of **7a**.

cycloaddition with a variety of dienophiles. In the case of **6c**, only the *exo* adduct was isolated; the *endo* adduct was found to decompose during purification. The reaction of **6e** with **5a** afforded an inseparable mixture of **7e** and **8e** in 3:1 ratio. The adducts obtained are potentially amenable to a number of synthetic transformations and can be manipulated to cyclooctanoid molecules of biological significance.

2.2. Chemistry of the α,β-unsaturated carbonyl part

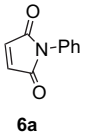
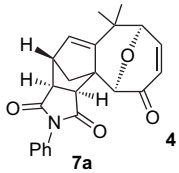
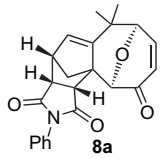
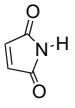
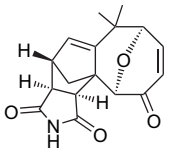
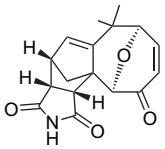
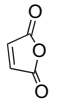
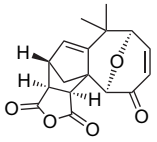
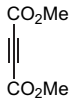
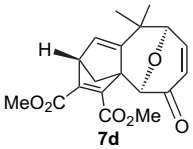
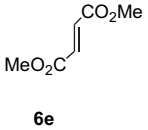
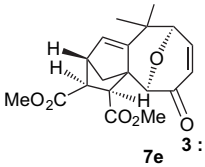
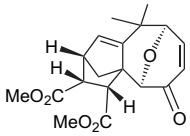
The α,β-unsaturated carbonyl group of the eight-membered ring is an easily functionalizable part and it is possible to add a new carbocyclic or heterocyclic ring to the molecule through appropriate transformations. Along this line, we have carried out the dipolar cycloaddition of the azomethine ylide[10] generated from *N*-methoxy methyl *N*-(trimethylsilylmethyl)benzylamine in the presence of trifluoroacetic acid. The reaction afforded the 5–8–5 fused system **10a** in 74% yield by selective reaction at the α,β-unsaturated ketone (Scheme 3).



Scheme 3.

The reaction was carried out with **5b** and **5c** and similar results were obtained (Table 2). The products **10a–c** have a unique 5–8–5 fused system, which can be manipulated

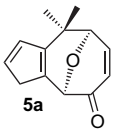
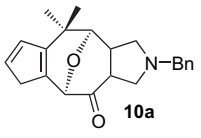
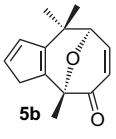
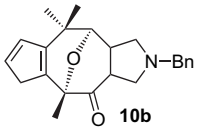
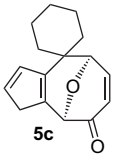
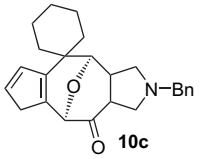
Table 1. [4+2] Cycloaddition of [6+3] adduct **5a** with some selected dienophiles

Dienophile	Products		Yield (%)
	exo Adduct	*endo* Adduct	
 **6a**	 **7a** 4 : 1	 **8a**	84
 **6b**	 **7b** 3.2 : 1	 **8b**	64
 **6c**	 **7c**		64
 **6d**	 **7d**		70
 **6e**	 **7e** 3 : 1	 **8e**	81

Reaction conditions: [6+3] adduct (1.0 equiv), dienophile (1.2 equiv), toluene, 50 °C, 8 h.

further towards bioactive molecules. By selecting a three carbon dipole such as oxyallyl cation or TMM, the corresponding 5–8–5 system analogous to the natural product kalmanol[11] (see Fig. 1) can be synthesized.

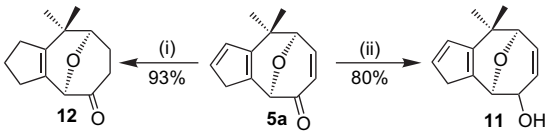
Table 2. Azomethine ylide addition to [6+3] cycloadduct

Entry	[6+3] Adduct	Product	Yield (%)
1	 **5a**	 **10a**	74
2	 **5b**	 **10b**	78
3	 **5c**	 **10c**	76

Reaction conditions: [6+3] adduct (1.0 equiv), **9** (1.2 equiv), TFA (catalytic), CH_2Cl_2, RT, 3 h.

2.3. Selective reduction

Luche reduction[12] of **5a** afforded the allylic alcohol **11** in 80% yield. The allylic alcohol **11** can be appropriately functionalized to the cyclooctanoid target of interest. On hydrogenation of **5a** over Pd/C at 1 atm, two disubstituted double bonds got reduced affording the product **12** with a tetrasubstituted double bond. The above transformations are illustrated in Scheme 4.

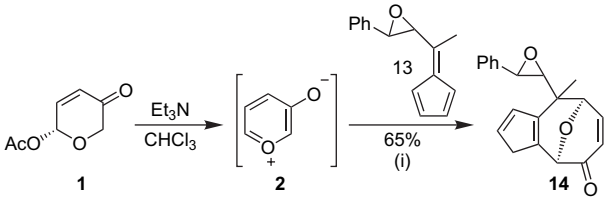


Scheme 4. (i) H_2 (1 atm), Pd–C (catalytic), ethyl acetate, rt, 6 h; (ii) $NaBH_4$ (3 equiv), 0.4 M Ce^{3+} in MeOH, rt, 4 h.

It is to be noted that the olefinic part of **12** can be readily opened leading to a 11-membered molecule analogous to that of neodolabelline natural products.[13]

2.4. Synthetic manipulations through C-6 functionalized fulvenes

We have also utilized functionalized fulvenes for the [6+3] cycloaddition with pyrylium betaines. The cycloaddition of 6-epoxyphenyl-6-methyl fulvene **13** with 3-oxidopyrylium betaine **2** afforded **14** in 66% yield (Scheme 5). The epoxide functionality of **14** can be opened with appropriate nucleophiles towards molecules similar to asteriscanolide (see Fig. 1).[14]



Scheme 5. (i) Fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

3. Conclusions

In conclusion, we have shown that 5–8 fused oxa-bridged molecules, obtained through [6+3] cycloaddition of fulvenes with 3-oxidopyrylium betaines, can be easily functionalized towards the synthesis of cyclooctanoid molecules of interest. The carbon framework of the molecules can be expanded directly from the product, thus enhancing the synthetic versatility of the products and these can act as key intermediates in the synthesis of fused cyclooctanoid natural products. It is presumed that by using appropriately functionalized fulvenes and oxidopyrylium betaines, the present methodology can be utilized in the synthesis of cyclooctanoid natural products. It is to be noted that some of the naturally occurring oxa-bridged cyclooctanoids, lancifodilactones, exhibit interesting biological activity such as cytotoxicity and anti-HIV activity.[15] In this context and in the general importance of fused cyclooctanoids, the methodology is very promising

and may lead to novel biologically active synthetic molecules. We have also shown that the 5–8 fused cyclooctanoid products are versatile molecules having multiple points for functionalization and can be synthetically manipulated easily. Further work along this line is in progress.

4. Experimental

4.1. General

All reactions were carried out in oven dried glassware under nitrogen atmosphere. Progress of the reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light or by staining with Enholm yellow solution. Column chromatography was done using 100–200 mesh silica gel and appropriate mixtures of petroleum ether (60–80 °C) and ethyl acetate for elution. The solvents were removed using a Buchi rotary evaporator. The IR spectra were recorded on Nicolet FT-IR spectrometer. NMR spectra were recorded on a Bruker FT-NMR spectrometer using $CDCl_3$ or $CDCl_3$–CCl_4 mixture (7:3) as solvent. TMS was used as internal standard and chemical shifts are in δ-scale. High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. Abbreviations used in ^{1}H NMR are: s, singlet; t, triplet; q, quartet and m, multiplet.

4.2. General procedure for the synthesis of compounds 7a–e and 8a–e

Dimethyl fulvene (250 mg, 2.36 mmol), pyranulose acetate (441.8 mg, 2.86 mmol) and dry triethylamine (285.8 mg, 2.86 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 5% ethyl acetate–hexane mixture as eluent to afford the [6+3] cycloadduct **5a** as a pale yellow crystalline solid (350 mg, 74%). The cycloadduct (100 mg, 0.50 mmol) was then treated with dienophile (0.55 mmol) in toluene at 50 °C in a Schlenk tube and stirred under nitrogen for 8 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue when subjected to chromatography on a silica gel (60–120 mesh) column using ethyl acetate–hexane mixture as eluent afforded the products in good yield.

4.2.1. Data for compounds 7a and 8a, total yield 84% (ratio 7a/8a=4:1).

4.2.1.1. Compound 7a. Colourless crystalline solid. Mp=232–234 °C. R_f (50% EtOAc–hexane) 0.47. IR (KBr) ν_{max}: 2959, 1776, 1708, 1498, 1376, 1187, 1067, 934, 866, 725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.28 (m, 5H), 7.11 (dd, 1H, J_1=4.2 Hz, J_2=10.6 Hz), 6.18 (d, 1H, J=2.8 Hz), 6.10 (d, 1H, J=10.6 Hz), 5.22 (s, 1H), 4.12 (d, 1H, J=3.7 Hz), 3.32 (s, 1H), 3.11 (d, 1H, J=6.8 Hz), 2.94 (d, 1H, J=7.23 Hz), 1.43 (m, 4H), 1.15 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 175.9, 149.7, 131.5, 129.2, 128.8, 126.6, 126.5, 75.4, 74.9, 53.1, 50.5, 48.0, 44.8, 43.9, 39.5, 30.3, 24.1. HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO_4$: 375.1471. Found: 375.1476. Anal. Calcd for $C_{23}H_{21}NO_4$: C 73.58, H 5.64, N 3.73. Found: C 73.69, H 5.57, N 4.05.

4.2.1.2. Compound 8a. Colourless crystalline solid. Mp=82–85 °C. R_f (50% EtOAc–hexane) 0.36. IR (KBr) ν_{max}: 2974, 2928, 1774, 1712, 1501, 1377, 1176, 1068, 929, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.17 (m, 5H), 7.03 (dd, 1H, J_1=4.2 Hz, J_2=10.5 Hz), 6.13 (d, 1H, J=2.8 Hz), 6.00 (d, 1H, J=10.5 Hz), 4.75 (s, 1H), 4.00 (d, 1H, J=4.0 Hz), 3.55–3.50 (m, 1H), 3.33 (d, 2H, J=7.9 Hz), 1.44–1.31 (m, 1H), 1.25–1.17 (m, 1H), 1.09 (s, 3H), 1.06 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 175.9, 175.1, 152.5, 150.5, 129.5, 129.0, 128.4, 126.2, 126.1, 79.1, 76.3, 56.6, 54.7, 52.1, 48.8, 43.5, 39.1, 30.1, 25.6. HRMS (EI) *m/z* calcd for $C_{23}H_{21}NO_4$: 375.1471. Found: 375.1478.

4.2.2. Data for compounds 7b and 8b, total yield 64% (ratio 7b/8b=3.2:1).

4.2.2.1. Compound 7b. Pale yellow viscous liquid. R_f (50% EtOAc–hexane) 0.30. IR (KBr) ν_{max}: 3232, 2922, 2855, 1715, 1468, 1339, 1270, 1190, 1102, 932 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.12 (dd, 1H, J_1=4.3 Hz, J_2=10.5 Hz), 6.13–6.08 (m, 2H), 5.17 (s, 1H), 4.11 (d, 1H, J=4.1 Hz), 3.23 (s, 1H), 3.00 (d, 1H, J=7.0 Hz), 2.83 (d, 1H, J=6.9 Hz), 1.45 (d, 1H, J=10.2 Hz), 1.38 (s, 3H), 1.16 (s, 3H), 1.10 (d, 1H, J=10.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.5, 177.8, 177.2, 153.1, 149.9, 130.9, 126.1, 75.1, 74.5, 52.0, 51.6, 49.0, 43.8, 43.6, 29.9, 23.8. HRMS (EI) *m/z* calcd for $C_{17}H_{17}NO_4$: 299.1158. Found: 299.1168.

4.2.2.2. Compound 8b. Pale yellow solid. Mp=231–233 °C. R_f (50% EtOAc–hexane) 0.29. IR (KBr) ν_{max}: 3227, 2979, 2876, 1769, 1712, 1686, 1351, 1192, 1068, 929 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.06 (dd, 1H, J_1=4.2 Hz, J_2=10.5 Hz), 6.05–5.97 (m, 2H), 4.66 (s, 1H), 4.03 (d, 1H, J=3.4 Hz), 3.41–3.36 (m, 1H), 3.14–3.11 (m, 2H), 1.45 (d, 1H, J=8.9 Hz), 1.25 (d, 1H, J=8.9 Hz), 1.23 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 176.8, 150.7, 148.4, 129.9, 125.6, 76.3, 75.7, 56.2, 55.4, 53.3, 49.5, 44.2, 43.5, 27.8, 22.6. HRMS (EI) *m/z* calcd for $C_{17}H_{17}NO_4$: 299.1158. Found: 299.1176.

4.2.3. Data for compound 7c. Pale yellow solid. Mp=247–249 °C. R_f (30% EtOAc–hexane) 0.14. IR (KBr) ν_{max}: 2974, 2938, 1779, 1687, 1498, 1223, 1083, 918, 862 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (dd, 1H, J_1=4.2 Hz, J_2=10.6 Hz), 6.15 (d, 1H, J=2.6 Hz), 6.08 (d, 1H, J=10.6 Hz), 4.99 (s, 1H), 4.11 (d, 1H, J=3.9 Hz), 3.33 (s, 1H), 3.27 (d, 1H, J=7.4 Hz), 3.11 (d, 1H, J=7.4 Hz), 1.36 (d, 1H, J=8.6 Hz), 1.35 (s, 3H), 1.16 (s, 3H), 1.13 (d, 1H, J=8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 173.5, 151.7, 149.8, 130.6, 125.1, 74.2, 73.5, 50.4, 48.9, 44.4, 43.9, 41.8, 29.3, 28.8, 22.9. HRMS (EI) *m/z* calcd for $C_{17}H_{16}O_5$: 300.0998. Found: 300.0970.

4.2.4. Data for compound 7d. Pale yellow solid. Mp=110–112 °C. R_f (30% EtOAc–hexane) 0.20. IR (KBr) ν_{max}: 2953, 2866, 1717, 1634, 1434, 1279, 1212, 1114, 1063, 1021 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (dd, 1H, J_1=4.3 Hz, J_2=10.5 Hz), 6.46 (d, 1H, J=2.9 Hz), 5.98 (d, 1H, J=10.5 Hz), 4.86 (s, 1H), 4.01 (d, 1H, J=3.9 Hz),

3.77 (s, 3H), 3.71 (d, 1H, J=4.3 Hz), 3.67 (s, 3H), 2.18 (d, 1H, J=6.9 Hz), 1.54 (d, 1H, J=6.9 Hz), 1.16 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 165.8, 164.3, 158.9, 155.3, 150.5, 149.2, 134.4, 126.2, 75.8, 72.2, 60.5, 52.5, 52.3, 49.5, 39.9, 29.4, 24.3. HRMS (EI) m/z calcd for $C_{19}H_{20}O_6$: 344.1260. Found: 344.1226.

4.2.5. Data for compounds 7e and 8e, *exo* and *endo* (3:1). Pale yellow viscous liquid. R_f (30% EtOAc–hexane) 0.23. IR (KBr) ν_{max}: 2953, 2871, 1738, 1702, 1434, 1382, 1259, 1068, 1017, 929, 867 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (dd, 1H, J_1=4.3 Hz, J_2=10.5 Hz), 6.05 (d, 1H, J=10.5 Hz), 5.91 (d, 1H, J=2.5 Hz), 4.33 (s, 1H), 4.07 (d, 1H, J=4.1 Hz), 3.80 (s, 3H), 3.65 (s, 3H), 3.44 (t, 1H, J=4.1 Hz), 3.16–3.10 (m, 2H), 1.83 (d, 1H, J=9.1 Hz), 1.42 (s, 3H), 1.13 (s, 3H), 0.94 (d, 1H, J=9.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 172.9, 172.8, 152.0, 149.9, 147.1, 129.4, 125.9, 123.0, 75.5, 52.1, 52.0, 51.7, 49.1, 47.1, 43.9, 39.1, 30.1, 23.8. HRMS (EI) m/z calcd for $C_{19}H_{22}O_6$: 346.1416. Found: 346.1421.

4.3. Typical procedure for the synthesis of compounds 10a–c

The cycloadduct **5a** (100 mg, 0.50 mmol) and *N*-methoxy methyl *N*-(trimethylsilylmethyl)benzylamine (130.6 mg, 0.55 mmol) were taken in anhydrous dichloromethane and cooled to 0 °C. A catalytic quantity of TFA was added and the mixture was stirred under an argon atmosphere for 4 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 20% ethyl acetate–hexane mixture as eluent to afford the product **10a** as a colourless viscous liquid (124 mg, 74%).

4.3.1. Data for compound 10a. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.58. IR (KBr) ν_{max}: 2964, 2917, 2799, 1717, 1568, 1449, 1367, 1078, 1022, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.16 (m, 5H), 6.39 (d, 1H, J=5.2 Hz), 6.29 (d, 1H, J=5.2 Hz), 4.54 (s, 1H), 3.54 (d, 1H, J=5.2 Hz), 2.99–2.85 (m, 5H), 2.74–2.68 (m, 4H), 2.46–2.41 (m, 1H), 1.29–1.19 (m, 3H), 1.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 148.4, 134.1, 130.4, 129.6, 129.1, 128.6, 127.6, 126.1, 79.2, 78.7, 76.4, 60.4, 55.5, 43.8, 40.7, 39.8, 30.4, 24.6, 23.7. HRMS (FAB) m/z calcd for $C_{22}H_{25}NO_2$: 335.1885. Found (M+1): 335.95.

4.3.2. Data for compound 10b. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.61. IR (KBr) ν_{max}: 2958, 2929, 2798, 1719, 1674, 1498, 1455, 1372, 1255, 1095, 1027, 856 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.12 (m, 5H), 6.43–6.14 (m, 2H), 3.72–3.51 (m, 3H), 2.96–2.88 (m, 5H), 2.73–2.65 (m, 3H), 1.48 (s, 3H), 1.39–1.19 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1, 148.0, 133.8, 130.3, 128.8, 128.6, 128.3, 128.1, 127.3, 127.2, 126.7, 79.5, 79.1, 60.1, 59.7, 59.4, 55.5. HRMS (FAB) m/z calcd for $C_{23}H_{27}NO_2$: 349.2042. Found (M+1): 350.19.

4.3.3. Data for compound 10c. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.67. IR (KBr) ν_{max}: 2930, 2858, 1718, 1671, 1454, 1375, 1185, 1151, 1080, 968 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–6.89 (m, 5H), 6.49–6.10 (m, 2H), 4.12 (d, 1H, J=4.8 Hz), 3.63–3.55 (m, 2H), 3.35–3.32 (m, 3H), 3.16–2.78 (m, 4H), 2.57–2.54 (m, 2H), 1.41–1.24 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.7, 133.4, 130.5, 129.3, 128.9, 128.6, 128.3, 128.2, 127.3, 76.9, 75.9, 72.9, 71.8, 60.1, 59.9, 55.1, 53.9, 49.7, 43.3, 40.5, 32.0, 29.3, 25.6, 22.4, 21.9. HRMS (FAB) m/z calcd for $C_{25}H_{29}NO_2$: 375.2198. Found (M+1): 376.22.

4.4. Typical procedure for the synthesis of 11

The cycloadduct **5a** (100 mg, 0.50 mmol) was dissolved in 0.4 M ceric nitrate solution in methanol and cooled to 0 °C. A stoichiometric amount of $NaBH_4$ (56.7 mg, 1.5 mmol) was added and the mixture was allowed to stir for 5 h at rt. The reaction mixture was quenched with water, the solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 30% ethyl acetate–hexane mixture as eluent to afford the product **11** as a colourless viscous liquid (82 mg, 80%).

4.4.1. Data for compound 11. Colourless viscous liquid. R_f (50% EtOAc–hexane) 0.32. IR (KBr) ν_{max}: 3412, 2964, 2907, 1624, 1383, 1274, 1171, 1073, 976, 914, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (d, 1H, J=4.2 Hz), 6.39 (d, 1H, J=4.2 Hz), 5.89–5.86 (d, 1H, J=10.5 Hz), 5.68–5.63 (d, 1H, J=10.4 Hz), 4.69 (d, 1H, J=6.0 Hz), 4.63 (s, 1H), 3.93 (d, 1H, J=1.5 Hz), 3.26–2.89 (m, 2H), 1.29 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 133.1, 131.7, 130.0, 129.3, 128.1, 75.9, 71.3, 67.0, 43.1, 38.8, 28.2, 23.4. HRMS (EI) m/z calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1002.

4.5. Typical procedure for the synthesis of 12

The cycloadduct **5a** (100 mg, 0. 50 mmol) was dissolved in anhydrous ethyl acetate. A catalytic amount of Pd–C (10%) was added and the reaction mixture was stirred under H_2 atmosphere at rt. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 10% ethyl acetate–hexane mixture as eluent to afford the product as a white crystalline solid (96 mg, 93%).

4.5.1. Data for compound 12. Colourless crystalline solid. Mp=107–110 °C R_f (50% EtOAc–hexane) 0.71. IR (KBr) ν_{max}: 2959, 2854, 1727, 1459, 1363, 1243, 1070, 1052, 888 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (s, 1H), 3.93–3.88 (m, 1H), 2.73–2.65 (m, 2H), 2.39–2.31 (m, 4H), 1.84–1.91 (m, 4H), 1.25 (d, 3H, J=5.4 Hz), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.3, 142.3, 129.1, 82.6, 75.1, 37.8, 35.3, 33.7, 31.5, 27.1, 22.7, 21.6, 21.1. HRMS (EI) m/z calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1330.

4.6. Typical procedure for the synthesis of 14

6-Epoxyphenyl-6-methyl fulvene (100 mg, 0. 48 mmol), pyranulose acetate (89.9 mg, 0.58 mmol) and dry triethylamine (58.6 mg, 0.58 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure

and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 5% ethyl acetate–hexane mixture as eluent to afford the product as a pale yellow viscous liquid (96 mg, 65%).

4.6.1. Data for compound 14. Yield 65%, pale yellow viscous liquid. IR (KBr) ν_{max}: 3067, 2928, 1690, 1610, 1497, 1376, 1246, 1158, 1066, 1012, 978 cm^{-1}. ^1H NMR: δ 1.30 (s, 3H), 2.95 (m, 2H), 3.69 (d, 1H, J=1.92 Hz), 3.77 (d, 1H, J=1.92 Hz), 4.64 (d, 1H, J=5.59 Hz), 4.81 (s, 1H), 5.99 (d, 1H, J=10.47 Hz), 6.38 (d, 2H, J=3.72 Hz), 6.95 (m, 1H), 7.32–7.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.2, 146.3, 137.1, 133.7, 133.6, 130.5, 129.3, 128.5, 128.1, 125.8, 125.6, 124.7, 124.6, 73.1, 68.5, 67.7, 56.1, 40.9, 29.3, 16.1. HRMS (EI) *m/z* calcd for $C_{20}H_{18}O_3$: 306.1256. Found: (M+) 306.1274.

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