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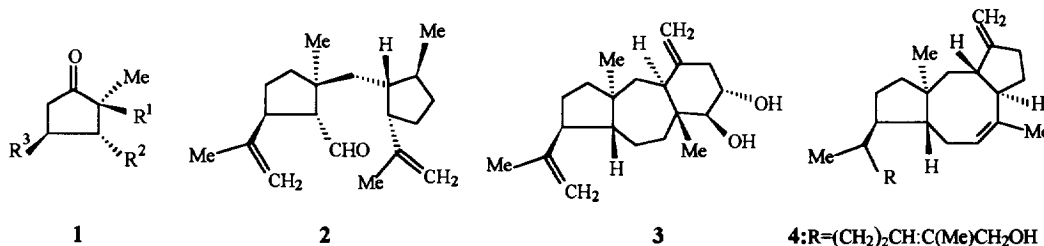
Intramolecular [2+2] Photocycloaddition - Cyclobutane Rearrangement. A Novel Stereocontrolled Approach to Highly Substituted Cyclopentanones[#]

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Abstract: A simple stereocontrolled route involving intramolecular [2+2] photocycloaddition followed by rearrangement of the resulting cyclobutane derivatives is described for the construction of cyclopentanones with substituents upto three contiguous chiral centres.

The synthetic and stereochemical problem associated with complex cyclopentanoid natural products provide ample scope for development of new methods¹ for the construction of cyclopentane rings. Many elegant strategies have been developed for the synthesis of vicinally substituted cyclopentanes². However, direct methods of constructing cyclopentanes³ of the general structure **1** with substituents on more than two contiguous carbon centres are scarce, despite the presence of these structural units in a wide range of natural

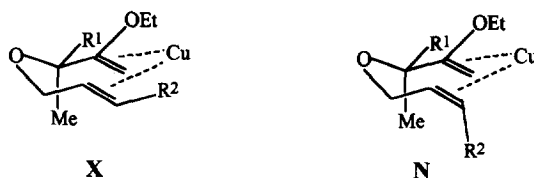


products e.g., dictymal **2**,⁴ clavularane **3**,⁵ ceroplastol **4**,⁶ etc. Herein, we report a direct stereocontrolled approach for the construction of cyclopentanones with substituents on three contiguous centres.

The key concept lies in the cuprous triflate (CuOTf) catalysed photocycloaddition of the diene **8** to form the cyclobutane derivative **9** followed by its stereospecific rearrangement involving central bond migration to the cyclopentanones **10** (Scheme 1).² It is the CuOTf catalysed cycloaddition that plays the pivotal role in determining the stereochemistry of the resulting cyclopentanones. As CuOTf catalyses E,Z-olefin isomerisation during irradiation, photocycloaddition of dienes e.g. **8** without the C₃-substituents normally⁸ produces a

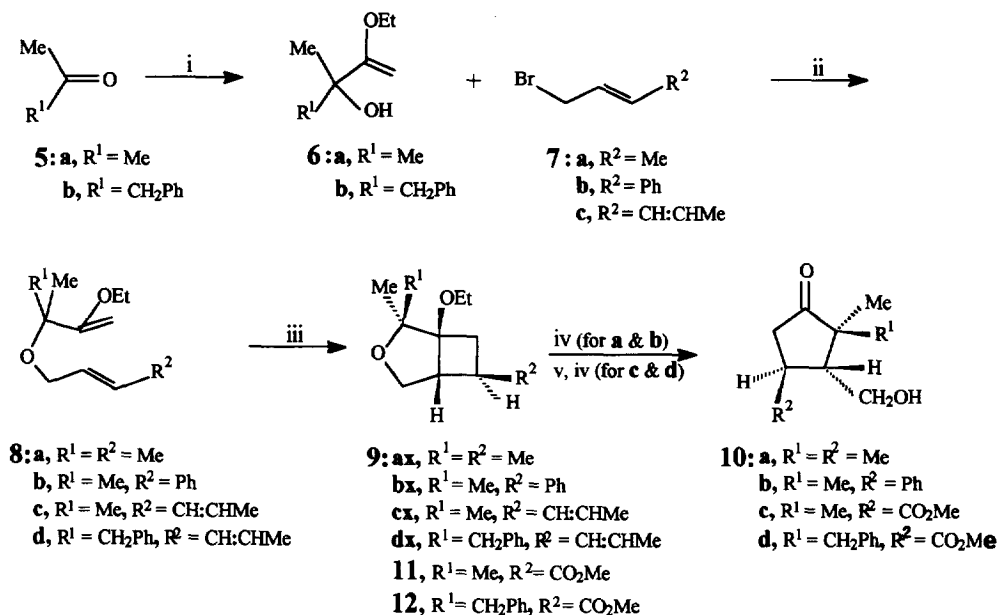
[#]Dedicated to Professor U. R. Ghatak on the occasion of his 65th birth anniversary

mixture of adducts arising from both *E* and *Z* isomers. We anticipate that with dienes **8** having the C_3 -substituents, the Cu(I)-diene complex **N**⁷ formed from *Z* isomer prior to photocycloaddition gets destabilised due to steric crowding between Me and R^2 inhibiting its formation. Furthermore, of the two C_3 -substituents the bulkier one prefers to occupy the *exo* position² in the Cu-complex. Photocycloaddition of the diene **8** is thus expected to produce the *exo* adduct **9** as the major product arising through the Cu-complex **X** derived from the *E*-isomer.



The dienes **8** required for this investigation were prepared from the ketones **5** on reaction with ethoxy vinyl lithium followed by coupling of the resulting carbinols **6** with the bromides **7**. Irradiation of an ether solution of the diene **8a** prepared from acetone, in the presence of CuOTf afforded a chromatographically inseparable mixture of the *exo* **8ax** and its corresponding *endo* cyclobutane derivative in ca. 2.5 : 1 ratio (GC). Treatment of this mixture with triflic acid (TfOH) effected smooth rearrangement to afford the cyclopentanone **10a** and its C_4 -epimer in a ratio nearly identical to that of the starting cyclobutanes. However, with the diene **8b** having a Ph at C_7 , photocycloaddition proceeded, to our expectation, with complete stereocontrol to produce exclusively a single adduct **8bx**⁹ (¹H and ¹³C) (53%). The *exo* stereochemical assignment to the adduct follows from its rearrangement to produce the single cyclopentanone derivative **10b** in 55% isolated yield. The *trans* relationship between the C_3 - and C_4 -hydrogens is established by the coupling constant ($J=11.6$ Hz), closely comparable to the coupling constant reported^{3b} for 1,2-disubstituted cyclopentanes. With the establishment of the structures of the cyclopentanone derivative **10b** and the cyclobutane derivative **9ax**, the major photoadduct and the major cyclopentanone obtained from the diene **8a** was assigned respectively the structures **9ax** and **10a**.

The general applicability and synthetic potential of this protocol is established by the synthesis of the cyclopentanones **10c** and **10d** as described below. The triene **8c** on irradiation in presence of CuOTf afforded a mixture of the *exo* cyclobutane derivative **9cx** and its corresponding *endo* isomer in ca. 2.2 : 1 ratio. Before carrying out the rearrangement, the double bond in the mixture of the photoadducts was oxidatively cleaved and the resulting acid mixture after esterification was equilibrated with refluxing NaOMe - MeOH to afford the thermodynamically more stable⁸ *exo* cyclobutane derivative **11** as the major product (58%). Rearrangement of the cyclobutane derivative **11** afforded the cyclopentanone **10c** (76%). On the contrary the triene **8d** afforded a single photoadduct¹⁰ (41%) to which the *exo* structure **9dx** was assigned based on its transformation to the cyclopentanone derivative **10d** through the cyclobutane ester **12**. The coupling constants between the C_3 ,



Scheme 1 Reagents and Conditions: i, Bu^tLi, ethyl vinyl ether, THF, -70^oC to rt, 80-95%; ii, NaH, THF, HMPA, reflux, 62-92%; iii, hv, Et₂O, CuOTf, 40-50%; iv, TfOH, CH₂Cl₂, -78^oC to rt. 52-76%; v, OsO₄, NaIO₄, Et₂O-H₂O; Jones oxidation, 0^oC; CH₂N₂, Et₂O; NaOMe-MeOH, reflux, 54 - 58%.

C₄-hydrogens of the cyclopentanones **10c** and **10d** respectively (10.6 and 11.0 Hz) dictates the trans stereochemical assignment of the substituents at these centres which in turn confirms the exo structures **9cx** and **9dx** for the cyclobutane derivatives. The resistance of the cyclopentanone ester **10d** to undergo epimerisation confirms this stereochemical assignment. The cyclopentanone derivative **10c** is suitably functionalised for elaboration to the gem-dimethylated natural products e.g. capnellene while the cyclopentanone derivative **10d**, because of its structural and stereochemical similarity, offers possibility for the synthesis of the terpenes **2 - 4**.

This investigation thus provides with an expedient stereocontrolled route to construct at the carbonyl carbon of appropriately chosen acyclic ketones, cyclopentanones with substituents upto three contiguous chiral centres.

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9. Selected spectral data: **9bx**, NMR: ^1H (200 MHz) 1.21(t, J=7Hz, 3H), 1.24(s, 3H), 1.40(s, 3H), 2.18-2.28(m, 1H), 2.68-2.97(m, 3H), 3.29-3.48(m, 2H), 3.68(d, J=9.6 Hz, 1H), 3.92(dd, J=4.8, 9.6 Hz, 1H) and 7.12-7.33(m, 5H); ^{13}C (DEPT) 15.7(Me), 21.3(Me), 24.7(Me), 32.1(CH₂), 36.1(CH), 52.9(CH), 59.2 (CH₂), 68.5(CH₂), 82.2, 85.1, 125.9, 126.6, 128.4, 129.1 and 145.5; **10b**, IR(neat): 1735, 3440 cm⁻¹; NMR: ^1H (200 MHz) 1.07(s, 3H), 1.25(s, 3H), 2.23 (partly resolved dt, J=6, 11.8 Hz, C₃-H), 2.42(dd, J=11.6, 18.8 Hz, 1H), 2.80(dd, J=8, 18.8 Hz, 1H), 3.07(dt, J=8, 11.6 Hz, C₄-H), 3.7(d, J=6Hz, 2H) and 6.41-7.55(m, 5H); **12**, IR(neat): 1735 cm⁻¹; NMR: ^1H (200MHz) 1.11(s, 3H), 1.24(t, J=7Hz, 3H), 2.43-2.63(m, 4H), 3.02-3.18 (m, 2H), 3.56(q, J=7Hz, 2H), 3.72(s, merged under a m at 3.64-3.77, total 4H), 4.13 (dd, J=5, 10Hz, 1H) and 7.17-7.31(m, 5H); ^{13}C (DEPT) 15.7(Me), 20.4(Me), 27.36(CH₂), 34.9 (CH), 36.9(CH₂), 47.9(CH), 51.9(OMe), 60.2(CH₂), 68.5(CH₂), 84.1, 87.0, 126.0, 127.8, 130.7, 138.4 and 175.1; **10d**, IR(neat) : 1735, 3480 cm⁻¹; NMR: ^1H (200 MHz) 1.03(s, 3H), 2.23(dd, J=18.8, 1H), 2.41-2.54(m, 1H), 2.58-2.71(m, 2H), 2.85(dt, J=7.7, 11 Hz, 1H), 3.09(d, J=13.6 Hz, 1H), 3.68(s merged with a m at 3.74, 5H) and 7.08-7.31 (m, 5H); ^{13}C (DEPT) 18.7(Me), 41.38 (CH₂), 41.45(CH), 42.4(CH₂), 47.0 (CH), 52.2(OMe), 53.1, 62.1(CH₂), 126.6, 128.3, 130.3, 137.1, 175.1 and 218.4; EIMS: m/z 276(M⁺), 258, 245, 199, 172, 145, 129, 114, 91(100%), 55 and 43.
10. The formation of a single photoadduct is possibly the result of destabilisation of the complex N by greater gem-dialkyl effect¹¹ of the C₃-substituents (Me, CH₂Ph in **8d** vs. Me, Me in **8a-c**) that pushes away the C₃-Me towards R².
11. cf. a) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719; b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.

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