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

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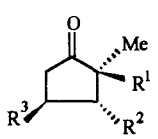
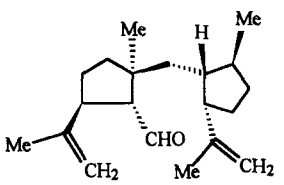
Abstract: *A simple stereocontrolled route involving intramolecular [2+2] photocycloaddition followed by rearrangement of the resulting cyclobutane derivatives is described for the construction of cyclopentanones with substituents upto three contiguous chiral centres.*

The synthetic and stereochemical problem associated with complex cyclopentanoid natural products provide ample scope for development of new methods[1] for the construction of cyclopentane rings. Many elegant strategies have been developed for the synthesis of vicinally substituted cyclopentanes[2]. However, direct methods of constructing cyclopentanes[3] 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



1



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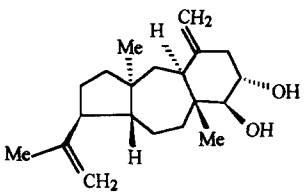

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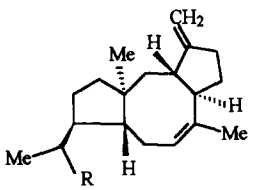


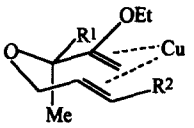
4:R=$(CH_2)_2CH{:}C(Me)CH_2OH$

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.

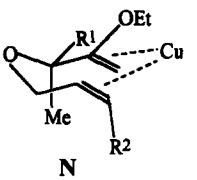
The key concept lies in the cuprous triflate (CuOTf) catalysed photocycloaddition of the diene **8** to form the cyclobutane derivative **9** followed by its stereospecific rearrangement involving central bond migration to the cyclopentanones **10** (Scheme 1).[2] It is the CuOTf catalysed cycloaddition 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 C_3 - substituents normally[8] 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 position[2] 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.



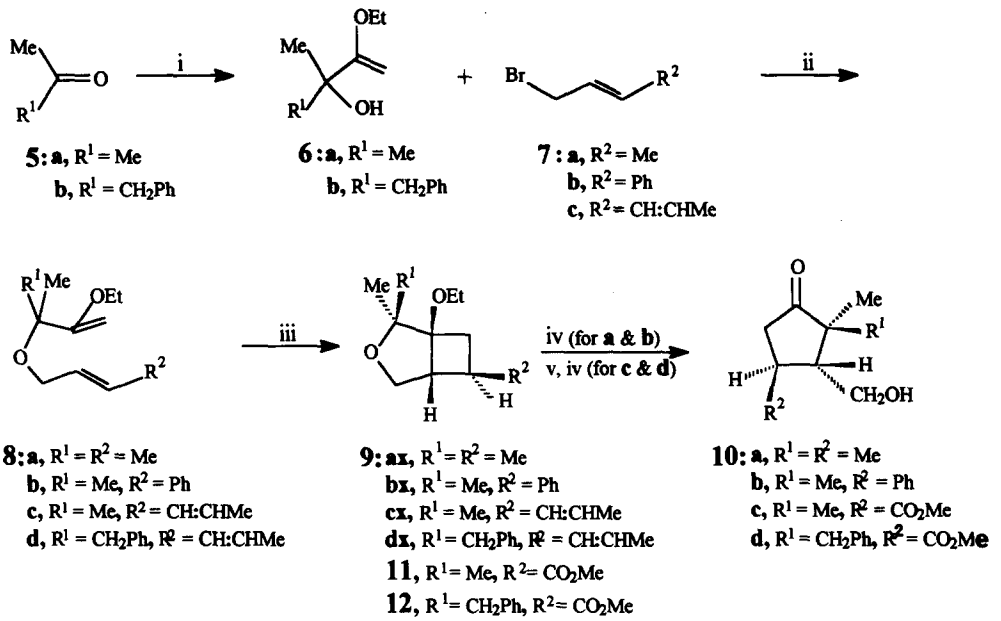
X



N

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 ^{13}C) (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 equilibriated with refluxing NaOMe - MeOH to afford the thermodynamically more stable[8] 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 photoadduct[10] (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^{t}Li, ethyl vinyl ether, THF, -70^{0}C to rt, 80-95%; ii, NaH, THF, HMPA, reflux, 62-92%; iii, hν, Et_2O, CuOTf, 40-50%; iv, TfOH, CH_2Cl_2, -78^{0}C to rt. 52-76%; v, OsO_4, $NaIO_4$, Et_2O-H_2O; Jones oxidation, O^{0}C; CH_2N_2, Et_2O; NaOMe-MeOH, reflux, 54 - 58%.

C_4-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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8. Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorski, M. *J. Am. Chem. Soc.* **1982,** *104,* 998.
9. Selected spectral data: **9bx,** NMR: ^{1}H(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(CH_2), 36.1(CH), 52.9(CH), 59.2 (CH_2), 68.5(CH_2), 82.2, 85.1, 125.9, 126.6, 128.4, 129.1 and 145.5 ; **10b,** IR(neat): 1735, 3440 cm^{-1} ; NMR: ^{1}H (200 MHz) 1.07(s, 3H), 1.25(s, 3H), 2.23 (partly resolved dt, J=6, 11.8 Hz, C_3-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, C_4-H), 3.7(d, J=6Hz, 2H) and 6.41-7.55(m, 5H) ; **12,** IR(neat): 1735 cm^{-1} ; NMR: ^{1}H(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(CH_2), 34.9 (CH), 36.9(CH_2), 47.9(CH), 51.9(OMe), 60.2(CH_2), 68.5(CH_2), 84.1, 87.0, 126.0, 127.8, 130.7, 138.4 and 175.1 ; **10d,** IR(neat) : 1735, 3480 cm^{-1} ; NMR: ^{1}H(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 (CH_2), 41.45(CH), 42.4(CH_2), 47.0 (CH), 52.2(OMe), 53.1, 62.1(CH_2), 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 effect [11] of the C_3-substitutents (Me, CH_2Ph in **8d** vs. Me, Me in **8a-c**) that pushes away the C_3-Me towards R^2.
11. cf. a) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahadron Lett.* **1992,** *33,* 6719 ; b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991,** *113,* 224.

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