Tetrahedron Letters,Vol.29,No.37,pp 4691-4694,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

INSIDE-OUTSIDE STEREOISOMERISM III[1]:

THE SYNTHESIS OF TRANS-BICYCLO[4.3.1]DECAN-10-ONE[+]

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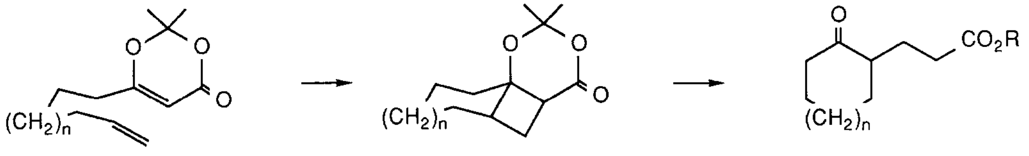
Summary: The synthesis of trans-bicyclo[4.3.1]decan-10-one, the smallest bicycloalkane to possess the inside-outside stereochemical relationship, is described, in which the trans intrabridgehead stereochemistry is established via the intramolecular dioxolenone photocycloaddition.

We have recently reported that the intramolecular photoaddition of dioxolenones to alkenes, i.e, 1--3,[5] leads to the formation of six-, seven- and eight-membered rings in good yield, and that this reaction can be applied to the synthesis of bicycloalkanes with the inside-outside intrabridgehead stereochemical relationship.[6,7] In this Letter, we describe the synthesis and characterization of trans-bicyclo[4.3.1]decan-10-one, 4, a compound which is ca. 20 kcal/mole more strained than the corresponding cis-bicyclodecanone, 5.



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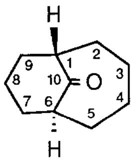

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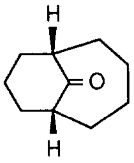

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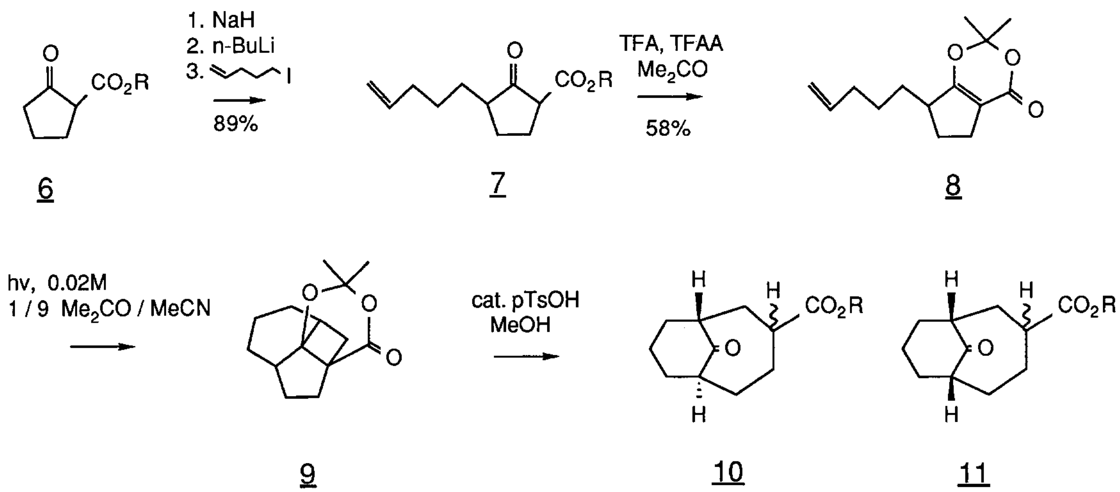
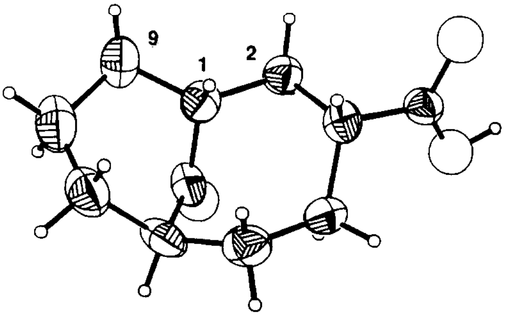
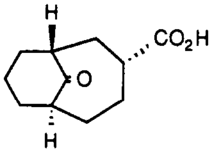
The photosubstrate 8 was prepared as outlined below.[8] Dianion alkylation[9] of t-butyl cyclopentanone 2-carboxylate[10] with 4-pentenyl iodide (89% yield), followed by dioxolenone formation (acetic anhydride, acetone, trifluoroacetic acid, room temp., 58% yield)[11] provided 8. In striking contrast to the irradiation of 12, which resulted in

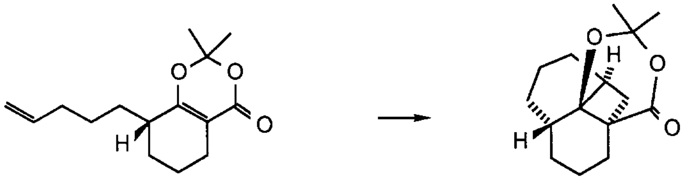


the exclusive formation of photoproduct, 13, with the inside-outside stereochemistry, irradiation of 8 (0.02M in 1:9 acetone/acetonitrile; pyrex immersion well; 0°C) for four hours resulted in the formation of two diastereomeric photoadducts, which, upon fragmentation (0.1 equivs. p-TsOH/methanol/reflux/72 hrs.), led to a 1:5 mixture of ketoesters 10 and 11 (as a mixture of epimers, vide infra) in 65% overall yield. To determine the intrabridgehead stereochemical relationships of 10 and 11, the separated ketoesters were submitted to ester hydrolysis (3 equivs. 1 M aqueous lithium hydroxide/methanol/tetrahydrofuran, 25°C), acid chloride formation (10 equivs. oxalyl chloride, catalytic dimethylformamide, benzene, 25°C, 1 h) and Barton decarboxylation (1.2 equivs. of the sodium salt of 2-mercaptopyridine-1-oxide, 0.1 equivs. dimethylaminopyridine, 10 equivs. tert-butyl thiol, diethyl ether, 100W sun lamp, two hours)[12] to provide the bicyclo[4.3.1]decanones, 4 and 5, respectively. Inspection of the ^{13}C NMR of these compounds led to the assignment of the major product, 5 [IR = 1692 cm^{-1} ($CHCl_3$); ^{13}C-NMR ($CDCl_3$): 19.6, 27.6, 31.7, 33.1, 48.7, 218.0] as the outside-outside *cis*-bridged compound and the minor product, 4 [IR = 1748 cm^{-1} ($CHCl_3$); ^{13}C-NMR ($CDCl_3$): 21.0, 25.5, 28.1, 29.3, 31.9, 34.9, 35.3, 49.5, 49.6, 219.1] as the *trans*-bridged stereoisomer, which contains neither a plane nor an axis of symmetry. Unambiguous proof for the inside-outside intrabridgehead stereochemical relationship followed from the single crystal X-ray analysis[13] of 10 (R = H), the most striking feature of which is that, to accomodate the inside-outside stereochemical relationship, the C9-C1-C2 bond angle in 4 is 130°.





The dramatic increase in strain energy difference between cis- and trans-bicyclo[5.3.1]-undecanones (ca. 10 kcal/mol) and cis- and trans-bicyclo[4.3.1]undecanones (ca. 20 kcal/mol)[14] leads to a striking difference in the stereoselectivity of the photocycloadditions of 8 and 12. In the photocyclization of 12, the exclusive formation of the inside-outside photoadduct, 13, was explained via a chair-like six-membered ring transition state in the photocycloaddition.[6] It was not expected that this orientation should be particularly sensitive to the ketoester ring size, i.e., 8 instead of 12. However, photocycloaddition of 8 results in the predominant formation of the "outside-outside" or cis-bridged bicyclic products. A later transition state for the photocycloaddition of 8 than 12, reflecting the difference in stability between the cis- and trans-bridged products, would account for the predominant formation of the more stable cis-bridged stereoisomer in the irradiation of 8.



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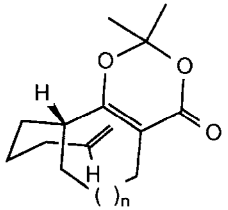

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In conclusion, we note again that the intramolecular photocycloaddition of dioxolenones has important advantages over the more classical deMayo diketone sequence.[15,16] Aside from the benefits of regiochemical control afforded by the use of the β-ketoesters, this new methodology makes possible the synthesis of trans-bicyclo[n.3.1]alkanones, which cannot otherwise be prepared.

Acknowledgements. Support from the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (CA40250 to J.D.W., GM35982 to P.G.W., and GM07148 in the form of a training grant fellowship to J.P.H.), the Alfred P. Sloan Foundation, an American Cancer Society Institutional Grant, and Merck, Sharp and Dohme is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

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\+ Dedicated to Professors Gerhard Closs and N. C. Yang on the occasion of their sixtieth birthdays.

1. For the previous paper in this Inside-Outside Stereoisomerism series, see J. Winkler, K. Henegar, P. Williard, *J. Am. Chem. Soc.*, *109* 2850 (1987).

2. Recipient of a Merck Grant for Faculty Development (1985-1986) and a National Institutes of Health Research Career Development Award (CA01337) (1988-1993). Fellow of the Alfred P. Sloan Foundation (1987-1989).

3. National Institutes of Health Predoctoral Trainee (GM07148).

4. Author to whom correspondence regarding the X-ray structure data should be addressed.

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13. Data were collected on a Nicolet R3m X-ray diffractometer. All crystallographic computations were carried out using the SHELXTL programs. Lattice constants a = 7.077(2) A, b = 6.361(2) A, c = 23.050(4) and β= 97.12(2)^{o}, monoclinic (P 2_1/a). R = 0.0615, R_w=0.0873.

14. Calculated using the Gajewski/Gilbert modification of the Allinger MM2 program (#395, Quantum Chemistry Program Exchange, Indiana University), which is commercially available through Serena Software, Bloomington, IN.

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(Received in USA 4 April 1988)