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A DIRECT ORGANOCOBALT MEDIATED SYNTHESIS OF SUBSTITUTED 3-OXABICYCLO[3.3.0]OCT-7-EN-6-ONES

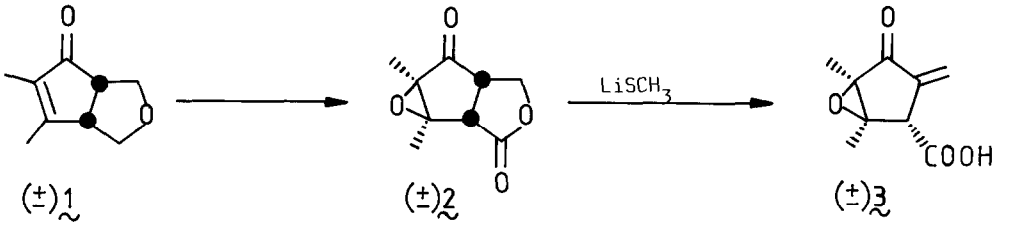
David C. Billington

Department of Pure and Applied Chemistry, University of Strathclyde,

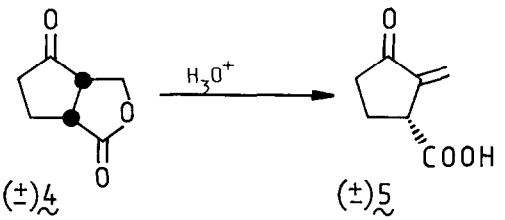
295 Cathedral Street, Glasgow G1 1XL

ABSTRACT: Substituted 3-oxabicyclo[3.3.0]oct-7-en-6-ones may be synthesised directly by reaction of alkyne hexacarbonyldicobalt complexes with 2,5-dihydrofurans; this strategy is illustrated by very brief total syntheses of cyclomethylenomycin A (2) and cyclosarkomycin (4).

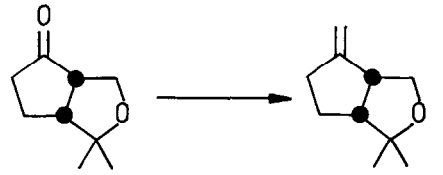
Substituted 3-oxabicyclo[3.3.0]oct-7-en-6-ones have been crucial intermediates in a number of natural product syntheses. In particular, the lactones derived from these compounds are readily converted into α-methylene-β-carboxyl substituted cyclopentenones, by ring opening and elimination. The antibiotic methylenomycin A (3), for example, has been synthesised from 3-oxabicyclooctenone (1) via the lactone cyclomethylenomycin A (2)[1], the anti-tumour agent sarkomycin (5) has been synthesised by hydrolysis of the lactone cyclosarkomycin (4)[2,3], and the iridoid monoterpene (7) has been prepared from the ketone (6).[4] Conventional approaches to substituted 3-oxabicyclo[3.3.0]oct-7-en-6-ones are lengthy (e.g. (1), 5 step synthesis;[1] (4), 7 step synthesis;[2] and (6), 10 step synthesis[4]) and are not easily modified to allow the synthesis of potentially biologically active analogues.



(±)1 (±)2 (±)3



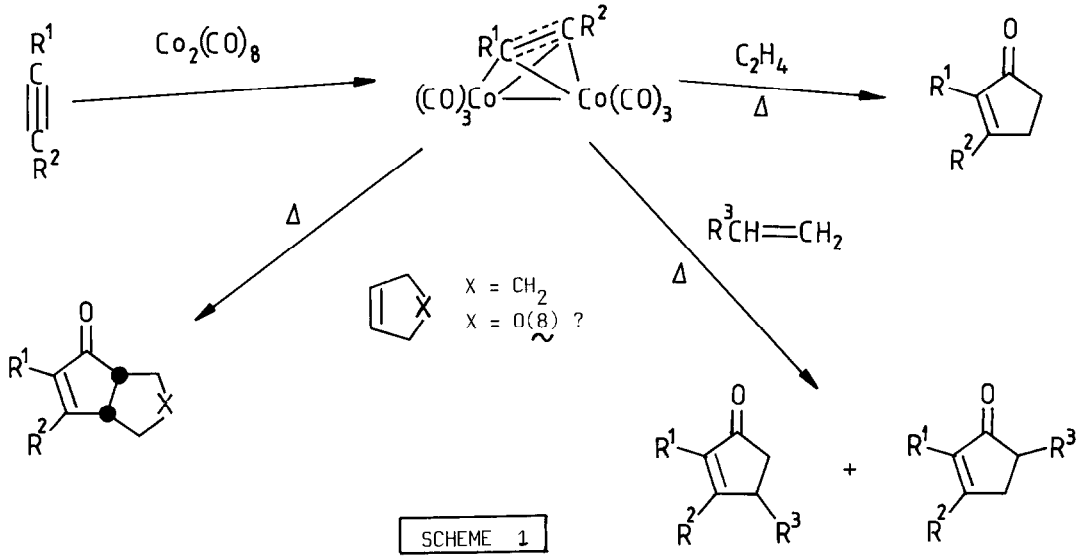
(±)4 (±)5



(±)6 (±)7

The condensation of an alkyne hexacarbonyldicobalt complex with an alkene, giving a cyclopentenone directly (Khand reaction[5]) seemed an ideal approach for the synthesis of the

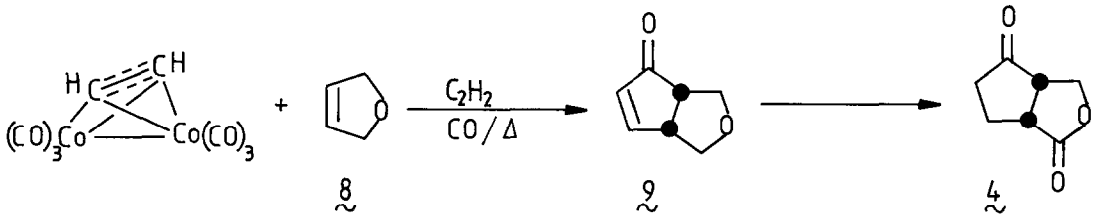
above bicyclic systems (Scheme 1). Alkyne hexacarbonyldicobalt complexes are available in almost quantitative yield from the requisite alkyne and $Co_2(CO)_8$,[5] and heating a solution of the complex concerned with an alkene gives a cyclopentenone in fair to moderate yield.[6] The reaction is regiospecific with respect to the alkyne fragment, the more bulky group on the alkyne appearing at C-2 of the product (R^1 larger than R^2 in the alkyne cf. Scheme 1),[7] but simple unsymmetrical alkenes normally give mixtures of C-4 and C-5 substituted products (R^3 in Scheme 1).[8] To date the Khand reaction has only found limited application in natural product synthesis.[9,5c] Our approach to the 3-oxabicyclooctenone skeleton involves the reaction of an alkyne hexacarbonyldicobalt complex with a 2,5-dihydrofuran, thus generating the bicyclic system directly (Scheme 1).



SCHEME 1

Treatment of a solution of (2- butyne)hexacarbonyldicobalt [available in 94% yield from 2-butyne and $Co_2(CO)_8$][9,10] in dry toluene, with 5 equivalents of 2,5-dihydrofuran (8) (Aldrich), followed by heating at 110°C for 8 h under nitrogen gave, after chromatography on alumina, the 3-oxabicyclooctenone (1) (Scheme 1, $R^1 = R^2 = CH_3$, X =O) in 15% yield.[11] Examination of a range of temperatures (70-100°C) and reactant ratios (complex:alkene, 1:5 → 1:35) improved this yield to 20%. The alkyne complexes are known to be thermally unstable, and their thermal decomposition is a serious problem at the elevated temperatures required for the cyclopentenone formation. This being the case we attempted to recycle the degraded complex by performing the reaction under an atmosphere of 50/50 2-butyne/carbon monoxide. Under these conditions, at 85°C with 20 equivalents of 2,5-dihydrofuran and using isooctane as solvent, 3-oxabicyclooctenone (1) was obtained in 37% yield after 3 days heating. Increasing the reaction time to 8 days resulted in isolation of (1) in 70% yield, based on consumed hexacarbonyldicobalt complex (50% recovery of (2-butyne)hexacarbonyldicobalt). 3-Oxabicyclooctenone (1) prepared by this route exhibits identical physical and spectral properties to those described by Smith, for (1) prepared by a 5 step conventional route.[1] Epoxidation of (1) with basic H_2O_2 (-20°C, 21 h, 85%)[1] followed by catalytic oxidation with RuO_4 (RT, 5 days, 43% yield)[1] gave cyclomethylenomycin A (2), identical with the material

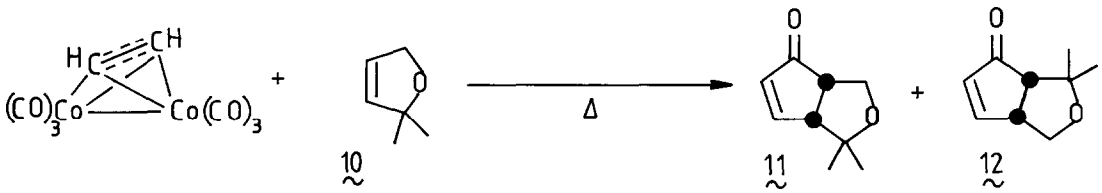
described by Smith.[1] 3-Oxabicyclooctenone (1) has also recently been a key intermediate in the synthesis of the related antibiotic desepoxy-4,5-didehydromethylenomycin A.[12]



8 9 4

Our initial approach to cyclosarkomycin (4) involved reaction of (ethyne)hexacarbonyldicobalt with 2,5-dihydrofuran (8) to generate 3-oxabicyclooctenone (9), which we hoped to convert to (4) via hydrogenation and catalytic RuO_4 oxidation.[1] As for the 2-butyne complex, non-catalytic (i.e. non recycling) conditions gave only a low yield of the desired 3-oxabicyclooctenone (9) whereas treating (ethyne)hexacarbonyldicobalt with 20 equivalents of 2,5-dihydrofuran in isooctane for 24 h at 65°C under an atmosphere of 50/50 ethyne/carbon monoxide gave (9) in 85% yield. Increasing the reaction time to 4 days gave (9) in a yield equivalent to 150% based on the starting hexacarbonyldicobalt complex. In this case therefore we are generating a 3-oxabicyclooctenone via a catalytic organocobalt reaction. The above reactions may also be successfully performed using $Co_2(CO)_8$ to generate the alkyne hexacarbonyldicobalt complex in situ (by reaction with the alkyne in the reaction atmosphere) rather than using the pre-formed complex. Hydrogenation of (9) (Pd on charcoal, ethanol, 97% yield) followed by catalytic oxidation using RuO_4[1] gave cyclosarkomycin (4) identical with the material described by Marx[2] and by Smith,[3] unfortunately in very low yield (>15%). Presumably this low yield indicates that substantial oxidative degradation is occurring under the reaction conditions, and we are currently examining alternative routes from (9) to (4) in the hope of defining an efficient synthesis of cyclosarkomycin, and hence sarkomycin.

In an attempt to synthesise the iridoid monoterpene precursor (6) the reaction between (ethyne)hexacarbonyldicobalt and 2,2-dimethyl-2,5-dihydrofuran (10) was examined.[13] In this case cyclisation only proceeded in very low yield (>12%) but, in contrast to the expected mixture of (11) and (12), a single regioisomer was obtained. On the basis of high field ^1H and ^{13}C n.m.r. we tentatively assign structure (12) to this material [i.e. the incorrect substitution pattern for elaboration to (7)].[14] In this reaction it appears that the gem-dimethyl group both inhibits the cyclisation, and directs the reaction towards the isomer in which the more bulky group on the alkene appears next to the carbonyl group.[15] We are currently investigating the effects which lead to this regioselectivity.



10 11 12

References and Notes.

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4. T. Imagawa, N. Murai, T. Akiyama and M. Kawanisi, Tetrahedron Lett., 1979, 1691; The length of this synthesis of (7) (11 steps) is quite representative of the synthetic challenge posed by even the simpler iridoid monoterpenes.
5. (a) I. U. Khand, G. R. Knox, P. L. Pauson and W. E. Watts, J.C.S. Perkin 1, 1973, 977; (b) P. L. Pauson and I. U. Khand, Ann. N.Y. Acad. Sci., 1977, 295, 2; (c) R. F. Newton, P. L. Pauson, and R. G. Taylor, J. Chem. Res., 1980 (S) 277; (M) 3501, and references therein.
6. A series of alkenes have been shown to participate in this reaction, including, ethene, norbornylene, cycloalkenes (C4 to C8), cyclopentadiene, etc. The cyclopentenone is presumably formed by insertion of one of the carbon monoxide ligands of an intermediate complex, in which both alkene and alkyne are bound to cobalt atoms, into a cobalt-carbon bond, followed by ring closure and release of the cyclic product.
7. I. U. Khand, and P. L. Pauson, J.C.S. Perkin 1, 1976, 30.
8. I. U. Khand, and P. L. Pauson, J. Chem. Res., 1977 (S) 9; (M) 168;
   A regiospecific reaction in which allyl tetrahydropyranyl ether is incorporated into a cyclopentenone giving only the C-5 substituted isomer has been reported; see reference 9.
9. D. C. Billington and P. L. Pauson, Organometallics, 1982, 1, 1560.
10. For a general preparative route see H. Greenfield, H. W. Sternberg, R. A. Friedel, J. H. Wotiz, R. Markby, and I. Wender, J. Am. Chem. Soc., 1956, 78, 120.
11. Yields refer to pure isolated products; All compounds gave satisfactory physical and spectroscopic (n.m.r., i.r. and mass) data.
12. D. Boschelli, R. M. Scarborough and A. B. Smith, Tetrahedron Lett., 1981, 22, 19.
13. The author wishes to acknowledge the assistance of Mr. William J. Kerr who performed these experiments.
14. ^{13}C Single Frequency Off Resonance Decoupled spectra clearly indicate the presence of a single regioisomer, and the tentative assignment of structure (12) is based on ^{1}H n.m.r. comparisons to other similar systems with known substitution patterns.
15. A similar directed reaction occurs for phenyl substituted norbornylenes, when the phenyl group appears adjacent to the carbonyl group in the product cyclopentenone; see reference 7.

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