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EFFICIENT SYNTHESIS OF SOME 2-OXASPIRO[3.5]NONA-1-ONES AS ANISATIN MODELS

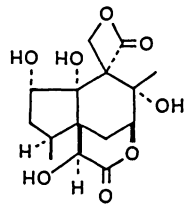
Michiharu KATO, Haruo KITAHARA, and Akira YOSHIKOSHI*
Chemical Research Institute of Non-Aqueous Solutions,
Tohoku University, Sendai 980

As a model study for the synthesis of anisatin, 2-oxaspiro[3.5]-nonane and 5-hydroxy-5-methyl-2-oxaspiro[3.5]nonane were synthesized from methyl cyclohexanecarboxylate and 2-ethoxycarbonylcyclohexanone, respectively, and these oxetanes were submitted to ruthenium tetroxide oxidation to afford the corresponding β-lactones.

Anisatin (1), the principal convulsive toxin isolated from seeds of Illicium anisatum L. (Japanese star anise), is a highly oxygenated sesquiterpenic β-lactone.[1]

Since the first paper of its model synthesis was published by Woodward et al.,[2] many efforts have still continued toward the synthesis of 1.[3]

β-Lactones are, in general, not only particularly susceptible to attack of both electrophilic and nucleophilic reagents producing ring cleavage products,[4] but also readily decompose to olefins and carbon dioxide on heating at moderate temperature.[5]



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Presence of such a reactive β-lactone ring in 1 led us consider the strategy that construction of this functional group should be carried out at as later stage as possible in the course of the synthesis of 1 and that the most viable synthetic precursor of 1 would be an oxetane because oxetanes are expected to be oxidized to β-lactones.

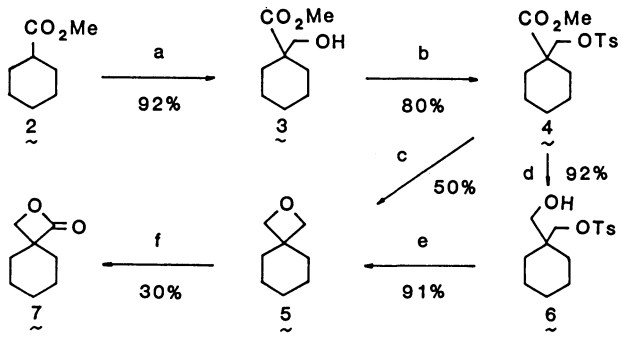
We report here a model study which would provide an efficient method for construction of 2-oxaspiro[3.5]nona-1-ones and would play a major role for the total synthesis of 1.

As shown in Scheme 1, we firstly tested the above plan by employing methyl cyclohexanecarboxylate (2) as a starting material, especially in order to verify whether oxidation of oxetane actually results in the formation of the desired β-lactone.

Trapping of the lithium enolate of 2 with gaseous formaldehyde led to formation of hydroxy ester 3,[6] which was then converted to the corresponding tosylate 4. In the hope that a tosyloxy alkoxide initially formed by preferential reduction of the methoxycarbonyl group in 4 with a metal hydride would lead oxetane 5[7] by successive internal nucleophilic displacement in a one-pot reaction, reduction of 4 with an equimolar amount of lithium aluminium hydride ($LiAlH_4$) was examined. When this reduction was performed at room temperature for 1.5 h, the major product was diol monotosylate 6 (92% yield), and in longer duration (15 h) it was over-reduction

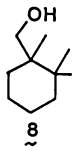
product 8 (59% yield). The expected oxetane 5 was always given in low yields. The best yield (50%) of 5 was obtained when the reduction was carried out with 0.5 molar equivalent of $LiAlH_4$ at 60 °C for 15 h.

It was reported that substituted oxetanes[8] and spirooxetanes such as 2-oxaspiro[3.2]hexane, 2-oxaspiro[3.3]-heptane, and 2-oxaspiro[3.4]octane[7a] underwent reductive cleavage of their oxetane rings with $LiAlH_4$ in boiling tetrahydrofuran, whereas 2-oxaspiro-[3.5]nonane (5) exceptionally resisted this reduction.[7a,9] Judging from this fact, our result mentioned above indicates that warming accelerated not only cyclization of the intermediate tosyloxy aluminium alkoxide to oxetane, but also caused the formation of 8 by concomitant hydrogenolysis of the tosyloxy group in 4.



a, (i)LDA,THF,-78 °C,(ii)CH_2O(g); b, p-TsCl,Py; c, $LiAlH_4$, THF,60 °C; d, $LiAlH_4$,THF,rt,1.5 h; e, NaH,THF; f, RuO_4, acetnoe.

Scheme 1.



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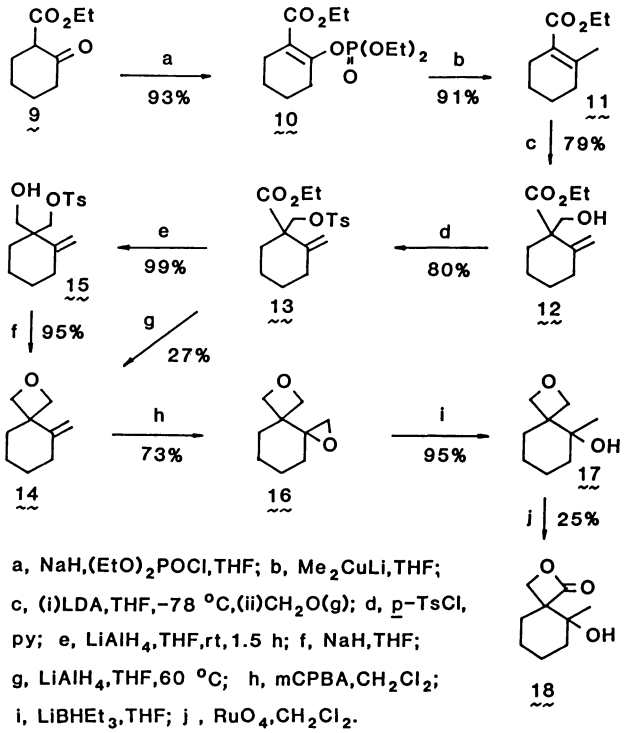
Since the preparation of 5 from 4 in a one-pot reaction turned out disappointing results, 6 was converted to 5 with base in excellent yield.

There is, to our knowledge, no report on ruthenium tetroxide oxidation of oxetanes. Having the oxetane 5 in hand, its oxidation with this reagent was carried out and the desired β-lactone 7[10] was isolated although in low yield.[11]

We next turned our attention to the synthesis of 5-hydroxy-5-methyl-2-oxaspiro[3.5]nona-1-one (18) from 2-carbethoxycyclohexanone (9) (Scheme 2). Ethyl 2-methyl-1-cyclohexene-carboxylate (11) was synthesized in high overall yield by enol phosphorylation of 9 followed by coupling of the resulting enol phosphate 10 with lithium dimethylcuprate.[12] Treatment of the lithium enolate of 11 with gaseous formaldehyde proceeded regioselectively to afford hydroxy ester 12 and the latter was converted into the corresponding tosylate 13. While attempted direct conversion of 13 to 14 by $LiAlH_4$ reduction similarly resulted in low yield, 14[13] was derived in excellent overall yield by treatment of 15, obtained in quantitative yield from 13 by $LiAlH_4$ reduction at room

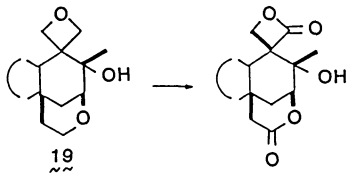


a, NaH,$(EtO)_2POCl$,THF; b, Me_2CuLi,THF; c, (i)LDA,THF,-78 °C,(ii)CH_2O(g); d, p-TsCl, py; e, $LiAlH_4$,THF,rt,1.5 h; f, NaH,THF; g, $LiAlH_4$,THF,60 °C; h, mCPBA,CH_2Cl_2; i, $LiBHEt_3$,THF; j , RuO_4,CH_2Cl_2.

Scheme 2.

temperature, with sodium hydride. Subsequent epoxidation of 14 with m-chloroperoxybenzoic acid proceeded smoothly to give epoxy oxetane 16[14] in high yield. Selective cleavage of the epoxide ring in 16 occurred by employing super hydride as a reducing agent, giving hydroxy oxetane 17[15] in almost quantitative yield.[16] On exposure to ruthenium tetroxide, the oxetane 17 gave the expected β-lactone 18[11,17] which was an inseparable 1:1 mixture of diastereomers as demonstrated by its NMR spectrum.

Although ruthenium tetroxide oxidation of 17, as seen, showed no regioselectivity, diether 19, a presumable progenitor of anisatin (1), can be expected to show a high stereoselectivity on oxidation of its oxetane ring owing to its oxabicyclo[3.3.1]nonane system.



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In conclusion, we have developed an efficient synthetic route for construction of the 2-oxaspiro[3.5]nona-1-one skeleton, which will be applicable to the synthesis of anisatin (1) as well as similar natural products.

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References

1) (Isolation) J. F. Lane, W. T. Koch, N. S. Leeds, and G. Gorin, J. Am. Chem. Soc., 74, 3211 (1952). (Structure) K. Yamada, S. Takada, S. Nakamura, and Y. Hirata, Tetrahedron, 24, 199 (1968). (Biological activities) S. Y. Chen, Am. J. Pharm., 101, 676 (1929).

2) D. L. Linder, J. B. Doherty, G. Shoham, and R. B. Woodward, Tetrahedron Lett., 23, 5111 (1982).

3) T. Mori, H. Niwa, and K. Yamada, 49th National Meeting of the Chemical Society of Japan, Tokyo, April 1984, Abstr., No. 2U32; T. Mori, H. Kuyama, S. Ito, H. Niwa, and K. Yamada, 50th National Meeting of the Chemical Society of Japan, Tokyo, April 1985, Abstr,, No. 3M11.

4) L. A. Paquette, " Principles of Mordern Heterocyclic Chemistry, " W. A. Benjamin, Inc., New York, N. Y. (1968), p.89.

5) H. E. Zaugg, Org. React., 8, 305 (1954); W. Adam, J. Baeza, and J-C. Liu, J. Am. Chem. Soc., 94, 2000 (1972); A. P. Krapcho and E. G. E. Jahngen, Jr., J. Org. Chem., 39, 1322 (1974).

6) All new compounds exhibited satisfactory physical properties (IR and ^{1}H NMR) and microanalytical data.

7) a) S. Searles, Jr., E. F. Lutz, and M. Tamres, J. Am. Chem. Soc., 82, 2932

(1960); b) S. Searles, R. G. Nickerson, and W. K. Witsiepe, J. Org. Chem., 24, 1839 (1959); c) E. J. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, J. Am. Chem. Soc., 82, 1218 (1960); d) P. Picard, D. Leclereq, J.-P. Bats, and J. Moulines, Synthesis, 1981, 550.

8) S. Searles, Jr., K. A. Pollart, and E. F. Lutz, J. Am. Chem. Soc., 79, 948 (1957); A. Rosowsky and D. S. Tarbell, J. Org. Chem., 26, 2255 (1961).

9) We have re-examined this reduction of 5 and recognized that 5 was mostly recovered unchanged along with a trace of 8 even on warming at 60 °C.

10) 7: IR ($CHCl_3$) 1820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-2.0 (m, 10H), 4.08 (s, 2H).

11) A small amount of the starting oxetane, 5 or 17, was recovered. On this oxidation of simple higher homologues, tetrahydrofurans and tetrahydropyrans give corresponding γ- and δ-lactones in less than 65% and 47% yields, respectively. A. B. Smith, III and R. M. Scarborough, Jr., Synth. Communs., 1980, 205.

12) L. Blaszczak, J. Winkler, and S. O'Kuhn, Tetrahedron Lett., 1976, 4405.

13) 14: IR (neat) 3060, 1645, 985, 895 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3-2.1 (m, 8H), 4.35 and 4.64 (d, J=5.4, 2H each, $-CH_2OCH_2-$), 4.65 and 4.83 (s, with fine splittings, 1H each, $=CH_2$).

14) 16: IR (neat) 985, 970, 923 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2-2.0 (m, 6H), 2.0-2.4 (m, 2H), 2.63 and 2.76 (d, J=4.3, 1H each, $-O-CH_2-$), 4.12 and 4.38 (d, J=5.4, 1H each, $-CH_2-O-CH_2-$), 4.32 and 4.56 (d, J=6.0, 1H each, $-CH_2-O-CH_2-$).

15) 17: IR (neat) 3400, 1120, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.1-2.2 (m, 9H), 4.23, 4.30, 4.68, and 4.83 (d, J=5.4, 1H each, $-CH_2-O-CH_2-$).

16) Reduction of this oxetane with $LiAlH_4$ produced a diol. Detail will be reported elsewhere.

17) 18: IR ($CHCl_3$) 3400, 1820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 and 1.42 (s, each, 3H in total), 1.0-2.2 (m, 9H), 3.90, 3.96, 4.47, and 4.58 (d, J=5.1, 0.5H each, $-OCH_2-$).

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