Stereospecific Synthesis of Carbocyclic Analogue of Oxazinomycin by Retrograde Aldol C–C Bond Fission under Reductive Conditions

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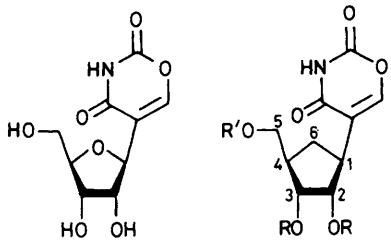
The Diels–Alder adduct prepared from cyclopentadiene and methyl (*E*)-3-acetoxy-2-cyanoacrylate (a newly synthesized dienophile) can be converted stereospecifically into the title compound using a retrograde aldol reaction under reductive conditions as a key step.

Oxazinomycin (minimycin)[1,2] is a *C*-nucleoside, produced by several *Streptomyces* species,[1—5] having antibacterial[3] and antitumour activities.[1,3] Its synthesis was achieved in a non-stereospecific manner from 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose by Bernardo and Weigele.[6]

We now report a novel synthesis of the carbocyclic analogue (**1**) of oxazinomycin from the Diels–Alder adduct of methyl (*E*)-3-acetoxy-2-cyanoacrylate, (*E*)-(**2**), and cyclopentadiene. The synthesis is characterized not only by the use of a newly synthesized dienophile (*E*)-(**2**), but also by the successful application of the retrograde aldol C–C bond fission under reductive conditions which was recently elaborated by our laboratory.[7,8]

The dienophile (*E*)-(**2**), m.p. 60—62 °C, was prepared in 76% yield by formylation of methyl cyanoacetate followed by acetylation. Though the primary acetylation product was the *Z*-isomer, (*Z*)-(**2**), m.p. 36—42 °C, it was transformed into (*E*)-(**2**) in quantitative yield by either heating slightly above its m.p. until it resolidified, or warming for a few hours in an appropriate aprotic solvent at about 50 °C.†

Diels–Alder reaction of (*E*)-(**2**) with an excess of cyclopentadiene without solvent at room temperature gave the adduct (**3**) as a mixture of *endo*- and *exo*-isomers (*ca.* 1:3) in quantitative yield. Oxidation of (**3**) with osmium tetraoxide in the presence of aqueous 60% 4-methylmorpholine 4-oxide occurred stereoselectively to form the *exo*-diol (**4**), which was treated with 2,2-dimethoxypropane in the presence of toluene-*p*-sulphonic acid in acetone to give the acetonide (**5**). Both reactions proceeded at room temperature in quantitative yield. When compound (**5**) was subjected to the retrograde aldol reaction under reductive conditions ($K_2CO_3/NaBH_4$ in MeOH; ice–salt cooling, 20 min), an almost quantitative yield of the desired product (**6**) was obtained with complete retention of the 1,4-*cis*-configuration.‡

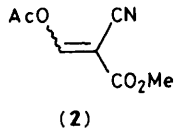


oxazinomycin

(**1**) R = R' = H

(**11**) R R = CMe_2

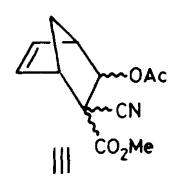
R' = $SiMe_2Bu^t$



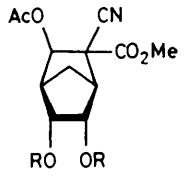
(**2**)

† ^1H δ_H ($CDCl_3$) (*Z*)—(**2**) 8.27; (*E*)—(**2**) 8.80.

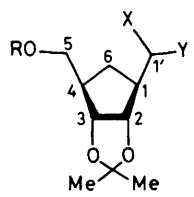
‡ Compounds (**6**)—(**9**) are mixtures of 1'-diastereoisomers.



(3)



(4) R = H
(5) RR = CMe_2



(6) X = CO_2Me, Y = CN, R = H
(7) X = CO_2Me, Y = CN, R = $SiMe_2Bu^t$
(8) X = CH_2OH, Y = CN, R = $SiMe_2Bu^t$
(9) X = CH_2OH, Y = $CONH_2$, R = $SiMe_2Bu^t$
(10) X = CHO, Y = $CONH_2$, R = $SiMe_2Bu^t$

The hydroxy group of (**6**) was protected by silylation (Bu^tMe_2SiCl, imidazole, Me_2NCHO) to give compound (**7**) in 90% yield. Selective reduction of the methoxycarbonyl group of (**7**) was carried out using sodium borohydride in methanol (cooled in ice) to give the alcohol (**8**) in quantitative yield. Alkaline hydrolysis (KOH, 30% H_2O_2, $Bu_4N^+HSO_4^-$) of (**8**) in dichloromethane at room temperature gave the amide (**9**) in 85% yield. Compound (**9**) was oxidized with dimethyl sulphoxide/dicyclohexylcarbodi-imide[9] in benzene at room temperature to give the formylacetamide (**10**),§ m.p. 99—100 °C (ether–hexane), in 58% yield. The oxazine-ring-forming reaction was accomplished by treatment of (**10**) with *N,N'*-carbonyldi-imidazole and sodium hydride in 1,2-dimethoxyethane at room temperature to give the protected carbocyclic oxazinomycin (**11**), m.p. 145—147 °C (from ether–hexane), in 86% yield. Deprotection of the hydroxy groups by treatment with 4 : 1 trifluoroacetic acid/water at room temperature completed the synthesis of (**1**) as colourless prisms (from ethyl acetate), m.p. 163—165 °C [$\lambda_{max.}$ (MeOH) 233 nm (log ε 3.65); $\nu_{max.}$ (Nujol) 1780sh, 1740sh, and 1710 cm^{-1}; δ_H ($CDCl_3/CD_3COCD_3$) 3.62 (2H, d, *J* 6 Hz, 5-H) and 7.56 (1H, s, oxazine 6-H)], in 85% yield. All compounds showed the expected spectroscopic properties and gave satisfactory combustion analyses or accurate mass measurement values.

§ Compound (**10**) exists as a mixture of keto and enol forms (*ca.* 3 : 8) in deuteriochloroform.

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References

1 T. Haneishi, T. Okazaki, T. Hata, C. Tamura, M. Nomura, A. Naito, I. Seki, and M. Arai, *J. Antibiot.*, 1971, **24**, 797.
2 K. Sasaki, Y. Kusakabe, and S. Esumi, *J. Antibiot.*, 1972, **25**, 44.
3 Y. Kusakabe, J. Nagatsu, M. Shibuya, O. Kawaguchi, C. Hirose, and S. Shirato, *J. Antibiot.*, 1972, **25**, 44.
4 K. Isouo and R. J. Suhadolnik, *Ann. N. Y. Acad. Sci.*, 1975, **255**, 390.
5 G. E. Gutowski, M. J. Sweeney, D. C. Delong, R. L. Hamill, K. Gerzon, and R. W. Dyke, *Ann. N. Y. Acad. Sci.*, 1975, **225**, 544.
6 S. De Bernardo and M. Weigele, *J. Org. Chem.*, 1977, **42**, 109.
7 C. Kaneko, N. Katagiri, M. Sato, M. Muto, T. Sakamoto, S. Saikawa, T. Naito, and A. Saito, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1283.
8 N. Katagiri, T. Haneda, and C. Kaneko, *Chem. Pharm. Bull.*, 1986, **34**, 4875.
9 G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, 1973, **38**, 1841.