Stereoselective Synthesis of the C-21 to C-27 Segment of Rifamycin-S

A. V. Rama Rao,* J. S. Yadav, and V. Vidyasagar

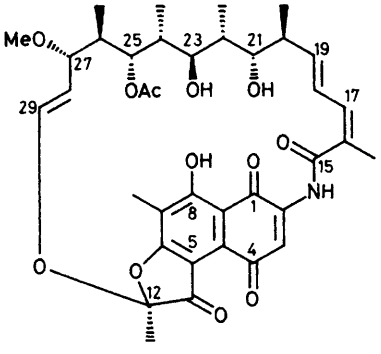
National Chemical Laboratory, Pune 411008, India

An efficient synthesis of the ansa chain of rifamycin-S corresponding to the C-21 to C-27 segment is described, starting from a bicyclic precursor *endo,endo*-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one.

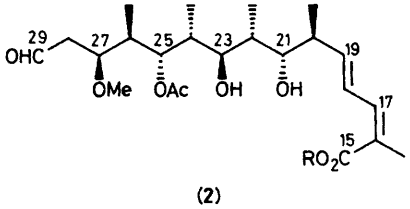
Rifamycin-S (**1**),[1] belonging to the novel ansamycin family of antibiotics has been a target compound for many synthetic chemists. After the first total synthesis of this antibiotic reported by Kishi and coworkers,[2] a number of papers have been published on the synthesis of the multichiral ansa chain (**2**) and the heavily substituted naphthoquinone moiety (**3**).[3] The acyclic stereocontrol approach by Kishi[4] towards its synthesis was an important step in natural product chemistry. Other notable synthetic strategies are Masamune's stereoselective aldol condensation,[5] Kinoshita,[6] Hannesian,[7] and Fraser Reid's,[8] approach to the molecule *via* carbohydrates, and Still's[9] stereoselective hydroboration method. In all the syntheses reported to date acyclic stereocontrol was the method of choice. In the present communication we report an approach to the ansa chain, which is different from the earlier reports, in that it employs a cyclic building block for the stereocontrolled functionalisation of the ansa chain.

The strategy was to build a cyclic molecule which (i) can be utilised for stereocontrolled functionalisation and (ii) should have a 'lock–key' system to cleave it to an acyclic unit. These two criteria were fulfilled by the bicyclic system (**4**) which has inherent rigidity for stereocontrolled functionalisation and an olefinic moiety with an α-ether linkage to serve as the 'key' to open the system.

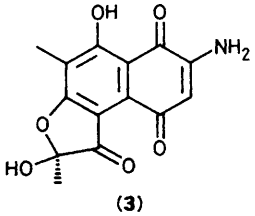
Cycloaddition of furan and the oxyallyl cation derived from 2,4-dibromopentan-3-one, according to the procedure of Hoffmann[10] afforded *endo,endo*-2,4-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one, (**4**), together with the two other diastereoisomers of (**4**). As the separation of (**4**) from its diastereoisomers was difficult at this stage,† the mixture was subjected to reduction by di-isobutylaluminium hydride to give the corresponding alcohols, from which the desired *endo* alcohol (**5**) was obtained by silica gel chromatographic separation (50% overall yield from dibromopentanone).‡ The alcoholic function in (**5**) was protected as its benzyl ether (**6**), [NaH–PhCH$_2$Br, tetrahydrofuran (THF), reflux, 90% yield]. The next stage was, by taking advantage of the olefinic bond, conversion of (**6**) into (**8**) *via* the alcohol (**7**). This was best achieved by hydroboration, followed by oxidation (BH$_3$–THF in diethyl ether, −10 °C, NaOH–H$_2$O$_2$) to yield the alcohol (**7**) in 95% yield. Oxidation of the alcohol (**7**) with pyridinium chlorochromate in methylene chloride at room temperature



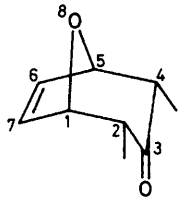
(**1**)



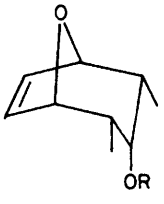
(**2**)



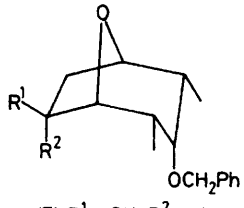
(**3**)



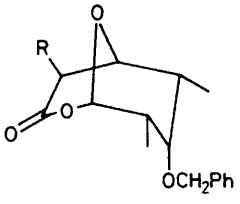
(**4**)



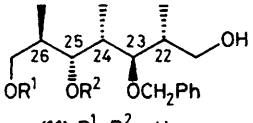
(**5**) R = H
(**6**) R = CH_2Ph



(**7**) R^1 = OH, R^2 = H
(**8**) R^1, R^2 = O



(**9**) R = H
(**10**) R = Me



(**11**) R^1, R^2 = H
(**12**) R^1, R^2 =

† Isomeric ketones have been separated earlier in pure form by g.l.c. (see ref. 10).

‡ Satisfactory elemental and spectral analyses were obtained for all the new compounds.

resulted in the formation of (**8**) in 93% yield. The carbonyl functionality in (**8**) serves a dual purpose; functionalisation of the α-carbon atom and a site for cleaving the cyclic moiety to the acyclic unit. Thus (**8**) was subjected to Baeyer–Villiger oxidation (CF_3CO_3H–Na_2HPO_4, CH_2Cl_2) to obtain lactone (**9**) in 80% yield (based on the recovered starting material). No trace of the other regioisomer was detected. Alkylation of (**9**) with lithium di-isopropylamide–MeI in THF–hexamethylphosphoramide at −78 °C led to isolation of exclusively the *exo* alkylated product (**10**) in 85% yield. [^{1}H n.m.r.: ($CDCl_3$) δ 0.95 (d, 3H, *J* 7.5 Hz), 1.10 (d, 3H, *J* 7.5 Hz), 1.45 (d, 3H *J* 8 Hz), 2.10 (m, 2H), 2.75 (q, 1H, *J* 8 Hz), 3.55 (distorted t, 1H, *J* 4.0 Hz), 3.66 (d, 1H, *J* 4.0 Hz), 4.55 (ABq, 2H, *J* 11 Hz), 5.37 (dd, 1H, ^1J 3, ^2J 1 Hz), and 7.29 (s, 5H)]. The fully functionalised unit (**10**) failed to undergo hydrolytic reaction under various conditions (NaOH, K_2CO_3, NaOMe, *etc.*). Finally the lactone (**10**) was subjected to exhaustive reduction to the tetrol monobenzyl ether (**11**), ($LiAlH_4$–diethyl ether, 3 h, −10 °C, and 2 h, room temperature), in excellent yield [^{1}H: ($CDCl_3$) δ 0.73 (d, 3H, *J* 7 Hz), 0.95 (d, 3H, *J* 7.0 Hz), 1.08 (d, 3H *J* 7.5 Hz), 1.55—2.25 (m, 3H), 3.35—4.10 (m, 6H), 4.65 (s, 2H), and 7.30 (s, 5H)]. Chemical differentiation of the two types of primary alcohol groups in (**11**) was carried out by protecting one of them in the form of acetonide (**12**) [2,2-dimethoxypropane–toluene-*p*-sulphonic acid, 90% yield, ^{1}H: ($CDCl_3$) δ 0.70 (d, 3H, *J* 7 Hz), 0.88 (d, 3H, *J* 7 Hz), 1.20 (d, 3H, *J* 7.5 Hz), 1.35 (s, 6H), 1.62—2.00 (m, 3H), 3.25—4.0 (m, 6H), 4.60 (s, 2H), and 7.22 (s, 5H)]. Compound (**12**) with five contiguous chiral centres representing C-21 to C-27 of the ansa chain having a primary alcoholic group serving as the 'handle' should serve as a key product for further elaboration.

Received, 4th September 1984; Com. 1261

References

1 P. Sensi, A. M. Greco, and R. Ballotta, *Antibiot. Ann.*, 1960, 262.
2 H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson, and Y. Kishi, *J. Am. Chem. Soc.*, 1980, **102**, 7962; H. Iio, H. Nagaoka, and Y. Kishi, *ibid.*, p. 7967.
3 H. Nagaoka, G. Schmid, H. Iio, and Y. Kishi, *Tetrahedron Lett.*, 1981, 899; K. A. Parker and J. J. Petraitis, *ibid.*, p. 397; T. R. Kelly, M. Behforouz, A. Echavarren, and J. Vaya, *ibid.*, 1983, 2331; M. Nakata, M. Kinoshita, S. Ohba, and Y. Saito, *ibid.*, 1984, 1373.
4 H. Nagaoka and Y. Kishi, *Tetrahedron*, 1981, **37**, 3873.
5 S. Masamune, B. Imperiali, and D. S. Garvey, *J. Am. Chem. Soc.*, 1982, **104**, 5528.
6 M. Nakata, H. Enari, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3283.
7 S. Hannesian, J. R. Pougny, and I. K. Boessenkool, *J. Am. Chem. Soc.*, 1982, **104**, 6164.
8 B. Fraser-Reid, L. Magdzinski, and B. Molino, *J. Am. Chem. Soc.*, 1984, **106**, 731.
9 W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, 1983, **105**, 2487.
10 H. M. R. Hoffmann, K. E. Clemens, and R. H. Smithers, *J. Am. Chem. Soc.*, 1972, **94**, 3940.