Tetrahedron Letters,Vol.26,No.18,pp 2173-2176,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF THE DIOXABICYCLONONANE UNIT OF TIRANDAMYCIN

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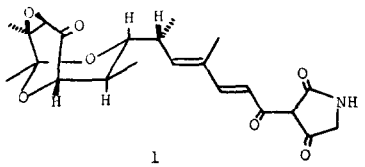
Summary: A seven-step synthesis of (±)-3b, an advanced, common intermediate for construction of the dioxabicyclononane units of both tirandamycin and streptolydigin from 14 is described (Scheme 1). Conversion of 3b to the fully developed fragment of tirandamycin is also reported.

Tirandamycin (1), streptolydigin (2) and their congeners constitute a small but growing family of natural products.[1] While their structures offer a number of synthetic challenges, construction of the dioxabicyclononane units and the attendant arrays of chiral centers



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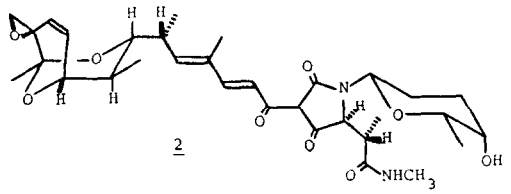
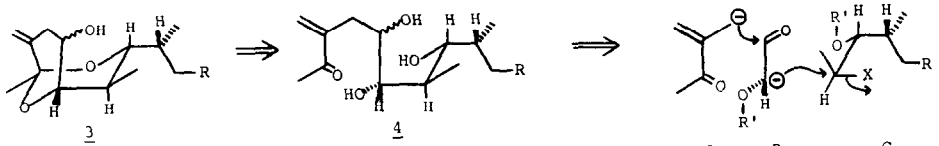


2

has attracted particular attention.[2] We now report the results of our efforts in this area.

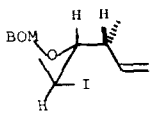
Compound 3 was selected as the initial target since it affords a branch point for the syntheses of both tirandamycin and streptolydigin. Analysis of the structure of 3 suggested that it might be produced by intramolecular ketalization of the trihydroxyketone 4. The



3 (a, R= =CH$_2$ b, R= OCH$_2$Ph) ⟹ 4 ⟹ A B C

latter was envisaged as being accessible by union of the generalized fragments A, B and C.

The initial synthesis of a C-type moiety was directed toward 5, with chirality ultimately deriving from (S)-ethyl lactate. Since (R)-ethyl lactate, however, is more readily available, the synthesis was developed in the antipodal series and is outlined in Equation 1.



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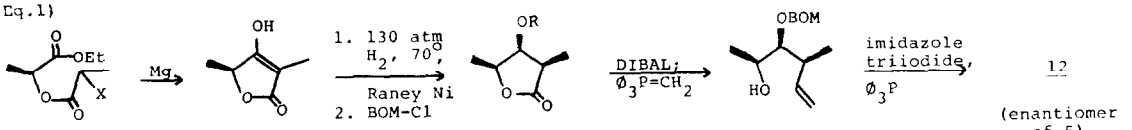
Thus 6, the α-bromopropionate derivative of (R)-ethyl lactate, was subjected to an intra-

(Eq.1)



6, X=Br
7, X=H

8

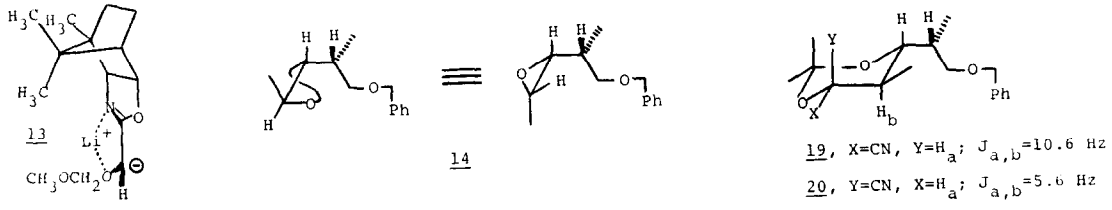
9, R=H
10, R=BOM

11

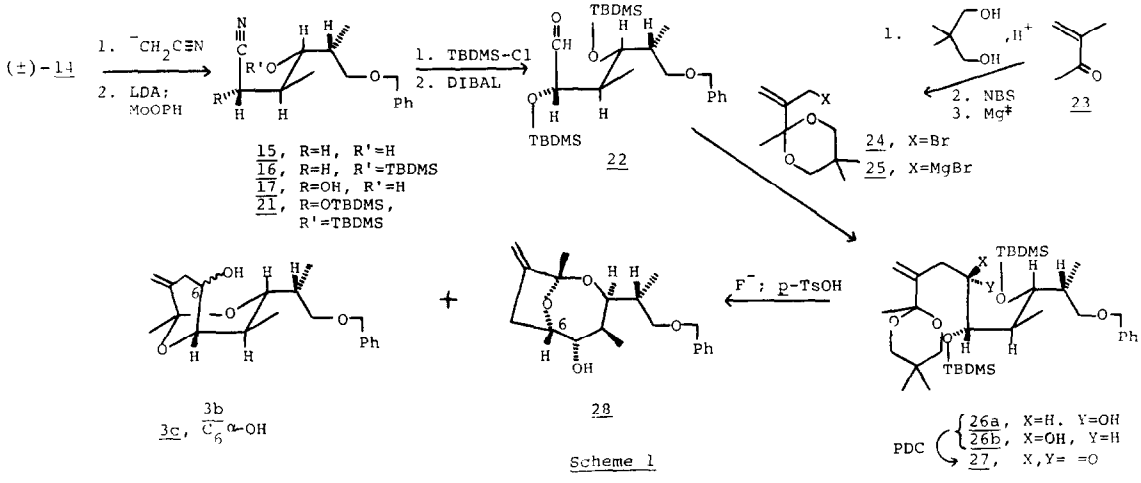
12 (enantiomer of 5)

molecular Reformatsky reaction to give the chiral[3] tetronic acid 8. Hydrogenation of 8 from the more accessible face introduced two new chiral centers, giving 9 with high stereochemical control. Protection of 9 as the benzyloxymethyl (BOM) derivative 10 was straightforward but the acronym proved a harbinger of things to come. DIBAL reduction followed without workup[4] by reaction with $\emptyset_3P{=}CH_2$ gave 11 which was converted to 12, the antipode of 5, with imidazole triiodide and triphenylphosphine.[5]

It was our intention at this point to couple 5 with 13, a compound which had been designed[6] as a chiral equivalent of the inherently achiral enolate of glyoxylic acid (fragment B). But while 13 is alkylated by a variety of simple alkyl halides with high ee, reaction of 13 with 12 failed under myriad conditions.[6] Iodide 12 also resisted displacement by numerous other nucleophiles. Accordingly, plans to use 5 were abandoned. Fortunately, however, report of a facile synthesis of (±)-14 had very recently appeared[7] and (±)-14 was enlisted as a stand-in for 5.



Epoxide 14 is also inert to 13 under a variety of conditions, but it does react smoothly with the anion of acetonitrile to give 15 (73%) which can be carried forward to the dioxabicyclononane unit of tirandamycin as outlined in Scheme 1. Thus hydroxylation[8] of 15 proceeds predominantly in the desired stereochemical sense to give 17 in 45% yield along with 30% of the undesired epimer (18); hydroxylation of the t-butyldimethylsilyl (TBDMS) ether 16 gave the unde-

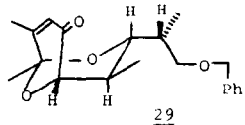


Scheme 1

sired stereoisomer as the principal (9:5, 70%) product [stereochemistry was assigned by conversion of 17 and 18 to the acetonides (20 and 19) and analysis of the vicinal coupling constants]. After protection as the bis TBDMS ether 21 (94%), DIBAL reduction gave (95%) aldehyde 22.

Completion of the carbon framework by reaction of 22 with the Grignard reagent derived from 24 was initially thwarted by the inertness of 24 toward conventional magnesium turnings and the propensity of 24 to suffer allylic dimerization in exemplary yield in the presence of Rieke[9]

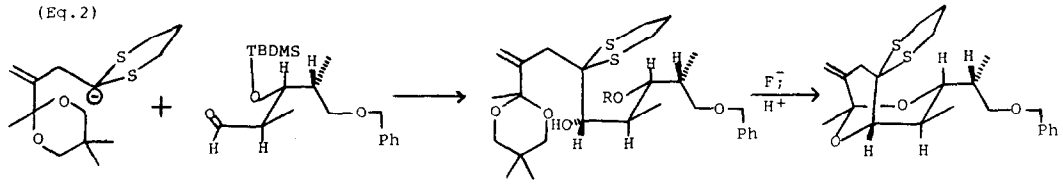
magnesium. But it was eventually found that addition of a 1:1 mixture of 22 and 24 to Rieke magnesium offered a gratifying solution to the impasse, giving 26 as a 2:1 mixture of epimers in 95% yield. Although the stereochemical outcome of the reaction had been anticipated to be immaterial, this expectation proved erroneous since to date only the minor stereoisomer has been carried forward productively. Specifically, treatment of the mixture of stereoisomers 26 with n-Bu_4NF and then p-TsOH converts the minor isomer to 3b and the major isomer to a product tentatively assigned structure 28 on the basis of spectral and mechanistic considerations. The assignment of stereochemistry to the 2° OH of 3b as in 3c, although of no lasting moment, follows if the structure of 28 (and the C-6 stereochemistry thereby demanded) are correct. The overall structure of 3c was confirmed by oxidation to the β,γ-unsaturated ketone and isomerization to the conjugated isomer 29, which proved identical by direct comparison to a sample of (±)-29 prepared by an independent route[2b] and provided by Professor P. Deshong. Cyclization of 27 to 29 or its deconjugated isomer could not be achieved. Conversion of 29 to tirandamycic acid has already been achieved.[2a,b]



29

The dioxabicyclononane unit was also achieved in a second route (Eq. 2) by cyclization of 33, which was prepared by coupling of aldehyde 32 (obtained by decomposition of the cyanohydrins produced by MoOPH oxygenation of 16) with the lithio dithiane 31 (prepared by alkylation of 2-lithio-1,3-dithiane with 24 followed by lithiation). Unfortunately, the dithioketal in 34 could not be hydrolyzed.

(Eq.2)



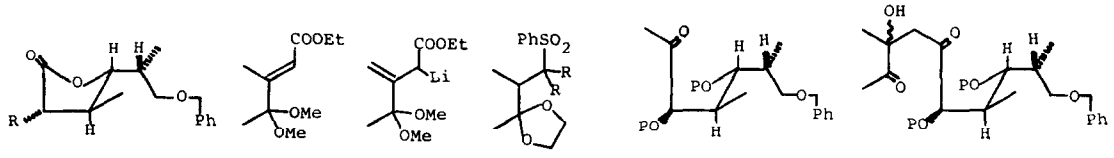
30, R=H
31, R=Li

32

33 (R=TBDMS)

34

An earlier approach to 29 entailed reaction of lactones 37 [prepared from 15 by hydrolysis



35, R=H 36, R=OH
37, R=OTBDMS, OMOM, OSEM

38

39

40, R=H
41, R=Li

42

43

P= acetonide, TBDMS, 2,4-dimethoxybenzyl

(→35), oxidation to 36 (LDA/MoOPH) and protection] with a variety of fragment-A synthons including 25, 39, and 41[10] but the adducts resisted further elaboration. Attempts to achieve intramolecular ketalization of triols derived from 43 [prepared by aldol condensation of 42 with $CH_3COCOCH_3$; 42 are available from 18 in two steps (protection and reaction with CH_3MgBr)] under conditions which could permit epimerization α to the ketone were unrewarding.[11,12]

Acknowledgments. Support of this work by a grant (GM28968) from the National Institutes of Health is gratefully acknowledged. We also thank Prof. Robert Dugger[2a] (Miami University) for exchange of information, Prof. Phil DeShong (Penn State) for a comparison sample and spectra of (±)-29 and other information, and Paula Wight for patience.

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2. Strategies conceptually similar to ours have been pursued in the laboratories of Dugger [Dugger, R.W., 185th National ACS Meeting, Seattle, March 1983, Abstract ORGN 6] and Bartlett [Bartlett, P.A., in "Selectivity - a Goal for Synthetic Efficiency", (Workshop Conferences Hoechst, Volume 14); Trost, B.M.; Bartmann, W., Eds.; Verlag Chemie: Weinheim, 1984; p 1; For other syntheses of the dioxabicyclononane unit of tirandamycin see a) Ireland, R.E.; Wuts, P.G.M.; Ernst, B. J. Am. Chem. Soc. **1981**, 103, 3205. (b) DeShong, P.; Ramesh, S.; Perez, J.J. J. Org. Chem. **1983**, 48, 217. (c) Ziegler, F.E.; Wester, R.T. Tetrahedron Lett. **1984**, 25, 617. (d) Martin, S.F.; Gluchowski, C.; Campbell, C.L.; Chapman, R.C. J. Org. Chem. **1984**, 49, 2512. For synthetic responses to other aspects see (e) Cartwright, D.; Lee, V.J.; Rinehart, K.L., Jr. J. Am. Chem. Soc. **1978**, 100, 4237. (f) Boeckman, R.K., Jr.; Thomas, A.J. J. Org. Chem. **1982**, 47, 2823. (g) DeShong, P.; Lowmaster, N.E.; Baralt, O. Ibid. **1983**, 48, 1149. (h) Kelly, T.R.; Kaul, P.N. Ibid. **1983**, 48, 2775.
3. Established by starting with (±)-ethyl α-deuterolactate (from ethyl pyruvate and $NaBD_4$) and showing that all the label remained in 8. Cyclization of 7 with NaH (53%) is apparently attended by some racemization. For a synthesis of (±)-8 using a different approach see Svendsen, A. and Boll, P.M. Tetrahedron **1973**, 29, 4251.
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11. All compounds gave spectra consistent with the assigned structure. Satisfactory combustion analyses were obtained for 3c, 10, 11, 15, 16, 19, 20, 21, 22, 24, 26, 27, and 28.
12. Salient experimental details. 6: 11.5g (R)-ethyl lactate + 10.5ml $CH_3CHBrCOBr$; 48 h at 22°→25.3g 6. 8: 2.53g 6 + 0.61g Mg + 25ml ether; 20 h at 22°; aq HCl/ether workup→ 55% 8. 9: 40g 8 in 170ml H_2O + ∿15ml W-2 Raney Ni; H_2, 130 atm, 70°, 29 h; filter through celite; concentrate; dissolve in CH_2Cl_2 and dry ($MgSO_4$) distil (bp 90°/0.2 mm) → 37g of a 91:5:4 mix of 9 and two diastereomers. 10: 2.44g 9 + 5.88g (i-Pr)$_2$NEt + 3.53g $PhCH_2OCH_2Cl$ 30 min at 0°; 24 h at 22°; nonaq workup; chromatography [silica, 3:7 EtOAc/pet ether ("p e^n")] → 2.62g 10. 11: 2g 10 in 50 ml toluene + 9.6mmol DIBAL in hexane; 3 h at -78°; 0.5 h at 22°; add rxn mix to 32 mmol $\phi_3P{=}CH_2$ in 100 ml THF; 20 h at 22°; aq HCl/ether workup; chromatography (silica, 3:2 benzene/ether) → 1.47g 11. 12: 0.11g 11 in 2.5ml toluene + 0.28g ϕ_3P + 0.24 g I_3Im; reflux for 15 h; aq $NaHCO_3/C_6H_6$ workup; chromatography (silica, 1:9 ether/p e) → 0.080g 12. 15: add 29.2ml CH_3CN to 0.564 mole LDA in 2L THF at -5°; after 10 min add 23g (0.2 eq) 14; 2h at -5°; 14h at 22°C; aq NH_4Cl/ether workup; LC (Waters Prep 500, silica, 1:1.3 ether/p e) →20.1g 15. 17: add 15.4 mmol 15 to 33.5 mmol LDA in 70ml THF at -78°C; after 30 min add 10g MoOPH; 15 min at -78°C; 2h at -23°C; aq $NaHSO_3$/ether workup; LC (silica, 1.6:1 ether/p e)→1.8g 17 + 1.15g 18. 19: 18 in acetone + 5 eq $Me_2C(OMe)_2$ + cat p-TsOH 16h at 22°C→20 (95%). 21: 0.5g 17 + 4.27g TBDMSCl + 4.05g imidazole + 20ml DMF; 10 days at 22°C; aq workup→0.881g 21. 22: 1.65g 21 in 125ml ether + 5.5ml 20% DIBAL in hexane; reflux 3h; aq H_2SO_4/ether workup→1.57g 22. 24: 14g 2-methoxy-5,5-dimethyl-1,3-dioxane [from $HC(OMe)_3$ + $HOCH_2C(CH_3)_2CH_2OH$] + 7g 23 + 30g $HOCH_2C(CH_3)_2CH_2OH$ + 50ml C_6H_6; 0°-5°, 16h; aq $NaHCO_3$/ether workup→13g 2-isopropenyl-2,5,5-trimethyl-1,3-dioxane (bp 77°/20mm); 2.01g of the dioxane + 2.1g NBS + 15mg Bz_2O_2 + 25ml CCl_4; reflux 40 min; filter; distil→2.24g 24 (bp 65°/0.2mm). 26: add mix of 0.94g 22 + 0.55g 24 in 18ml THF to Mg (from 2.5g $MgCl_2$ + 1.83g K) in 65 ml THF, 0.24ml/min (syringe pump) at -10° - -15°; then -5° for 15 min; aq NH_4Cl/ether workup→1.2g 26. 3c + 28: 0.286g 26 + 1g n-$Bu_4NF\cdot 3H_2O$ in 25ml THF; 2h at 22°; workup; dissolve crude product in 40ml THF + ca 15mg p-TsOH;48h at 22°; aq $NaHCO_3$/ether workup; chromatography (silica, 3:2 p e/ether)→40 mg 3c + 80 mg 28. 29: 70mg PDC + 100mg 4A molec sieves + 2ml CH_2Cl_2 30 min at 22°; add 30mg 3c in 2ml CH_2Cl_2; 2h at 22°; filter (celite); concentrate; stir in 10ml ether with 2g silica gel 1h at 22°; filter and concentrate →30mg 29. 30: 2-lithio-1,3-dithiane (0.5M in THF) + 1eq 24; 3-4h at -78°; aq NH_4Cl/ether workup→85% 30. 32: 16(R=OH) and/or its epimer in ether (5% soln) + 5 eq 1N NaOH; 2h at 22°→100% 32. 33: 0.74g 30 in 35ml THF + 0.43ml TMEDA + 1.1ml 2.6M n-BuLi in hexane; 3h at -50°; 1h at -30°: cool to -78°; add 0.90g 32 in 2ml THF; 10 min at -78°; aq NH_4Cl/ether workup; chromatography (silica, 12:88 EtOAc/p e)→1.23g 33 (mix of epimers). 34: 0.70g 33 + 1g n-$Bu_4NF\cdot 3H_2O$ + 75ml THF; 2h at 22°; aq workup; chromatography (silica, 4:1 p e/EtOAc)→0.15g less polar diol (33a,) + 0.36g more polar diol; 0.15g 33a in 40ml THF + ca 15mg p-TsOH; 16h at 22°; aq $NaHCO_3$/ether workup→102mg 34. 35: 6.72g 15 in 100ml MeOH + 10.5ml conc HCl; reflux 5h; remove solvent in vacuo; add 90ml H_2O + 130ml satd $NaHCO_3$; 10h at 22°→ 6.5g 35. 36: add 12.2g 35 in 25ml THF to 54mmol LDA in 600ml THF; 15 min at -78°; add 27g MoOPH; 2.5h at -78°; aq $NaHSO_3$/ether workup; LC (silica, 1:1 ether/p e)→1.5g 35 + 5.4g 36 + 2.3g epimer of 36. 38: add 1.7g $(EtO)_2P(O)CH_2COOEt$ to 0.18g NaH in 20ml THF; 1h at 22°; add 1g $CH_3C(OCH_3)_2COCH_3$; 2h at 22°; aq workup; distil →1.26g 38 (bp 85°-90°/4mm). 40: 3.7ml 23 + 9g $C_6H_5SO_2Na$ + 2g AcOH + 22ml 95% EtOH; 17h at 22°; aq $NaHCO_3$/ether workup→7.5g ketosulfone 40a; 7.5g 40a in 50 ml C_6H_6 + 3.5ml $HOCH_2CH_2OH$ + 20mg p-TsOH; reflux 40h (Dean-Stark); aq. $NaHCO_3$/ether workup→8.3g 40. 42 (acetonide): 19 in 1:1 THF/toluene + 5 eq CH_3MgBr in ether; reflux 10h; add excess aq NH_4Cl: stir at 22° for 30 min; extract with ether→95% yield. 43 (acetonide): add 42 in THF to 1 eq LDA (ca 1M in THF) at -78°; 15 min at -78°; then add 1 eq diacetyl in THF all at once; 5 min at -78°; aq NH_4Cl/ether workup→95% yield. Other 42's and 43's prepared analogously.

(Received in USA 29 January 1985)