for **1a** and **1b**. The m values are listed in Table II for comparison.

Depression of the data points corresponding to log k's measured in low nucleophilic solvents from the linear relationship (eq 1) defined by those measured in relatively high nucleophilic solvents, such as the cases of *tert*-butyl bromide[11] and 1,1,1-trifluoro-2-methyl-2-propyl triflates,[12] has been attributed to the assistance by the latter solvents. Although different interpretation had been given to the *tert*-butyl system,[13] a more recent rebuttal[14] confirmed the validity of the original proposal.[11] Therefore, the deviation showed in Figure 1 could be explained similarly. In the solvolysis of **1a** a significant acceleration by nucleophilic solvents is revealed in association with the large difference between m_{TE} and m_{AEM} (0.25).[15] This acceleration effect is so large that the steric prohibition of solvent intervention by an *o*-CH_3 group makes **2** to be less reactive than **1a** in nucleophilic solvents. Furthermore, the observed excellent linear correlation for log ks in all solvents (R = 0.996) and the small difference between various m values (0.05 or less) also suggest the absence of significant nucleophilic solvent acceleration.

The steric ortho effect might be of different origin.[16] In the solvolysis of **2** the steric hindrance to the π resonance in the cationic transition state is likely to be relatively unimportant, for an *o*-methyl group in the corresponding chlorides has been found to give a 3.6-fold increment of the solvolytic reactivity.[9] It is likely due to the steric hindrance to the solvation of cationic transition states. The solvation, and probably the solvent acceleration, will be less significant for the substrate having a better leaving group.

The influence of an electron-releasing substituent can be shown by comparing the different degree of deviation in log k – Y plots. Excellent linear relationships have been observed for both the *p*-CH_3 derivative **1b** and the *p*-SCH_3 derivative **1c** (R > 0.996). However, the small splitting between m_{TE} and m_{AEM} observed for **1b** (0.11)[15] and a negligible one for **1c** (0.05) suggest a small acceleration is still present in the former but is essentially absent in the latter. Obviously the more stable the cationic transition state involved, the less acceleration due to nucleophilic solvent would be necessary.

Although the application of the multiple regression analysis (eq 2)[17] of log k_{1a} against Y_{BnOPNB}[5] and N_{OTS}[7] values gave an improved correlation (m = 0.857, l = 0.298 and R = 0.976), no significant azide effect[18] could be detected in this study. It is in line with the recent conclusion

$$\log (k/k_o) = mY + lN \qquad (2)$$

by Richard and co-workers[2] and thus suggests that the nature of the solvent acceleration should be different from the classical S_N2 type interaction. From the recent recognition of the importance of the solvation effect on delocalized cationic transition states for benzylic substrates,[3-5,19,20] the acceleration is likely the result of an enhanced solvation by nucleophilic solvents. In the acidic and electrophilic TFE,[21] a cation will be poorly solvated,[22] and therefore the depression of ks is resulted. For the more reactive substrates, the solvolytic transition states will be of less cationic character. In addition, steric hindrance to the adjacent reaction site will diminish the importance of solvation (vide supra). In either case smaller extent of rate enhancement by nucleophilic solvents would be expected and indeed was observed.

Consequently, from the present kinetic study the intervention of nucleophilic solvents to enhance the solvolytic reactivity for *tert*-cumyl *p*-nitrobenzoates can be proved. The electronic effect of substituents on the aryl ring[1] cannot be the sole origin responsible for the change of solvolytic reactivities. More work to find out if this is a generalization to other substrates is in progress.

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(11) Bentley, T. W.; Bowen, C. T.; Parker, W.; Watt, C. I. F. *J. Am. Chem. Soc.* **1979**, *101*, 2486.
(12) Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1981**, *103*, 3863.
(13) For example, Fărcasiŭ, D.; Jähme, J.; Rüchardt, C. *Ibid.* **1985**, *107*, 5717.
(14) Bentley, T. W.; Roberts, K. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1055.
(15) The lower value of m_{TE} is likely due to the larger difference in nucleophilicity, and hence the rate-hancement, between ethanol and trifluoroethanol.
(16) For reviews see: (a) Charton, M. *Progr. Phys. Org. Chem.* **1971**, *8*, 235. (b) Fujita, T.; Nishida, T. *Ibid.* **1976**, *12*, 49.
(17) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700.
(18) For examples of pioneered work, see: (a) Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *Ibid.* **1971**, *93*, 4281. (b) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46.
(19) Bentley, T. W.; Dau-Schmidt, J.-P.; Llewellyn, G.; Mayr, H. *J. Org. Chem.* **1992**, *57*, 2387.
(20) Bentley, T. W.; Koo, I. S.; Norman, S. J. *Ibid.* **1992**, *56*, 1604.
(21) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 1050.
(22) Marcus, Y. *Pure Appl. Chem.* **1983**, *55*, 977.

Synthesis of the Polyol Chain of (–)-Roxaticin

Scott D. Rychnovsky*[,1] and Cesar Rodriguez

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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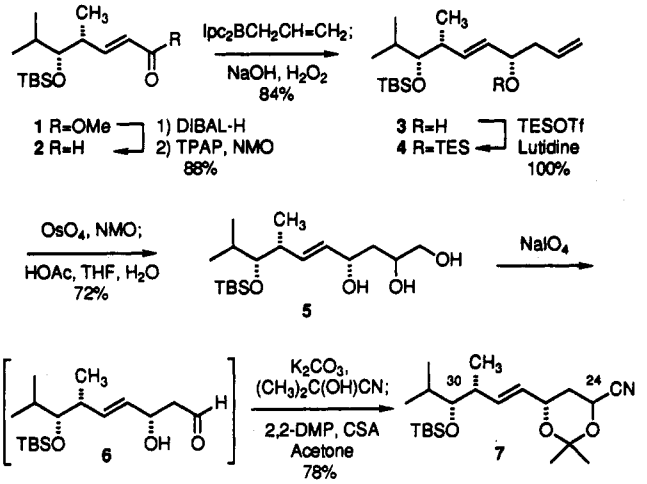
Summary: Tetraacetonide **19**, which incorporates the 10 stereogenic centers of (–)-roxaticin, was chosen as a test case to develop a convergent synthesis of alternating polyol chains. This synthesis uses a stepwise alkylation of dibromide **16** followed by a stereoselective reductive decyanation in a three-fold convergent strategy.

Complex polyol chains are important structural components of the polyene macrolide antibiotics such as the antifungal agent amphotericin B.[2] Several of these

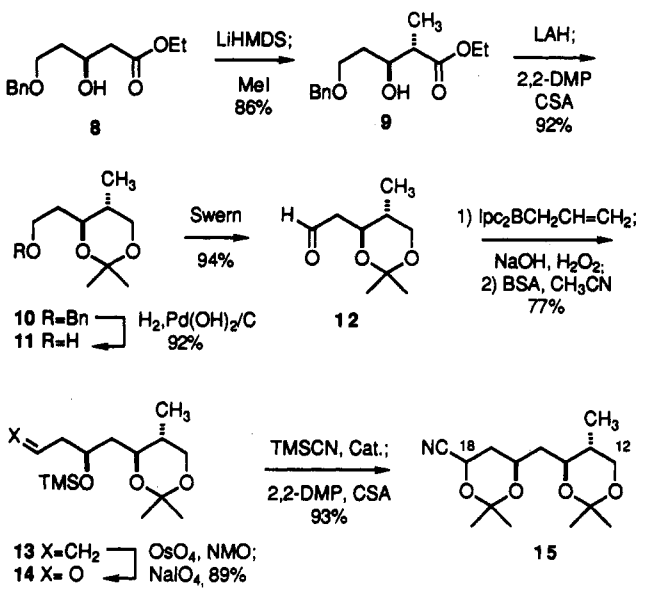
(1) Camille and Henry Dreyfus Teacher–Scholar 1990–1995. Alfred P. Sloan Research Fellow 1992–1993. McKnight Land-Grant Professorship, 1990–1993.
(2) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351–404.

0022-3263/92/1957-4793$03.00/0

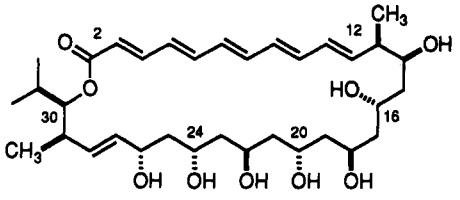
Scheme I



Scheme II



polyene macrolide antibiotics have been synthesized in the past few years,[3] and a wide variety of related synthetic methods have been developed.[4] Our interest in the mode of action of polyene macrolide antibiotics[5] lead us to search for a practical synthesis of these compounds that would be suitable for the preparation of structural analogs.[6] Roxaticin,[7] a relatively simple polyene macrolide antibiotic, was chosen as a target with which to develop new synthetic strategies. We report herein a three-fold convergent strategy for synthesis of the polyol portion of (-)-roxaticin.



(-)-Roxaticin

(-)-Roxaticin is a pentaene macrolide with 10 stereogenic centers located in the C(12)–C(30) section. The tetraacetonide **19** contains the C(12)–C(30) section and is a projected synthetic precursor to (-)-roxaticin itself. Compound **19** can be dissected into three fragments of comparable complexity, compounds **7**, **15**, and **16**, where the substituents on these fragments were chosen to facilitate assembly using our cyanohydrin acetonide couplings.[6b] This strategy should be very efficient by virtue of its 3-fold convergence and lends itself to the preparation of structural analogs by fragment substitution. The C(24)–C(30) fragment **7**, the C(23)–C(19) fragment **16**, and the C-(12)–C(18) fragment **15** must each be prepared in optically pure form. We have previously reported the preparation of dibromide **16**.[6c] The syntheses of nitriles **7** and **15** are illustrated in Schemes I and II, respectively.

Synthesis of the C(24)–C(30) fragment **7** begins with the unsaturated ester **1**. Ester **1** was prepared according to the method of Helquist[8] from isobutyraldehyde by an enantioselective boron aldol reaction, TBS protection, reduction, and Wittig reaction. DIBAL-H reduction and Ley's catalytic perruthenate oxidation[9] gave the corresponding aldehyde **2** in 88% overall yield. The remaining stereogenic center was introduced by allyl addition using Brown's allyldiisopinocampheylborane ($Ipc_2BCH_2CH{=}CH_2$) reagent prepared from (*R*)-(+)-α-pinene.[10] The resulting alcohol was protected as a triethylsilyl (TES) ether, oxidized with catalytic OsO_4 and 1.05 equiv of *N*-methylmorpholine *N*-oxide (NMO),[11] and hydrolyzed with 2:2:1 THF/HOAc/H_2O at 23 °C for 3 h. Triol **5** was obtained in 72% yield by this procedure, whereas the direct oxidation of **3** gave triol **5** in only 11% yield accompanied by a mixture of products arising from oxidation of the internal alkene. The bulky TES group acts to hinder the internal alkene rather than to suppress reactions of the alcohol. Oxidation of triol **5** with $NaIO_4$ produced the β-hydroxy aldehyde **6** which was used without further purification. Cyanide exchange from acetone cyanohydrin catalyzed by K_2CO_3, followed by treatment with acetone, 2,2-dimethyoxypropane (2,2-DMP), and camphorsulfonic acid (CSA) gave cyanohydrin acetonides **7** as a 1:1 mixture of isomers at the cyanohydrin center in 42% overall yield from ester **1**.[12] The mixture of isomers is of no conse-

(3) Amphotericin B: (a) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2205–2208. (b) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2208–2210. (c) Nicolaou, K. C.; Chackraborty, T. K.; Ogawa, Y.; Daines, R. A.; Simpkins, N. S.; Furst, G. T. *J. Am. Chem. Soc.* **1988**, *110*, 4660–4672. (d) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chackraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685. (e) Nicolaou, K. C.; Daines, R. A.; Chackraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696. (f) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chackraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705. 19-Dehydroamphoteronolide B: (g) Kennedy, R. M.; Abiko, A.; Takenasa, T.; Okumoto, H.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 451–454. Pimaricin: (h) Duplantier, A. J.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7079–7081.

(4) For a recent review of these methods see: Oishi, T.; Nakata, T. *Synthesis* **1990**, 635–645.

(5) Mickus, D. E.; Levitt, D. G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 359–360.

(6) (a) Rychonovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982–4984. (b) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550–5551. (c) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. S. *J. Org. Chem.* **1991**, *56*, 5161–5169. (d) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563.

(7) Maehr, R.; Yang, R.; Hong, L.-N.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816–3819.

(8) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988–3992.

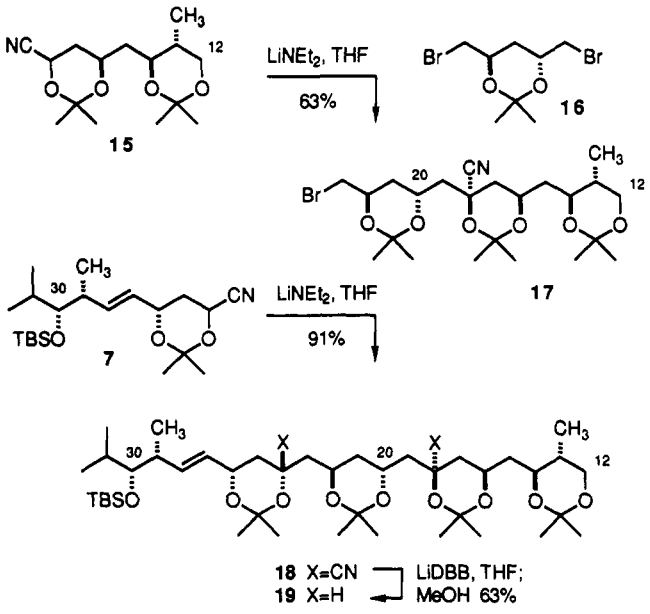
(9) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

(10) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 423–439. (c) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–404.

(11) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.

(12) The two nitrile epimers of compounds **7** and **15** can be separated by chromatography, but were normally used as a mixture. In the case of compound **7**, the syn isomer had an R_f of 0.24 in 10% ethyl acetate/hexanes whereas the anti isomer had an R_f of 0.34 in the same solvent system.

Scheme III



quence as the C(24) stereogenic center is reset in the next step.

Synthesis of the C(12)–C(18) fragment **15** begins with the optically pure alcohol **8**. Alcohol **8** was prepared by enantioselective hydrogenation of the corresponding β-keto ester as described by Noyori.[13] The corresponding dianion was generated by treatment of **8** with LiHMDS in THF at −78 °C followed by warming to 0 °C. Frater–Seebach alkylation[14] with MeI gave a 10:1 mixture of anti to syn stereoisomers, where the anti isomer **9** was isolated in 86% yield. Reduction with LAH in THF, followed by treatment with acetone, 2,2-DMP, and CSA gave acetonide **10**. The benzyl group was removed by hydrogenation with Pearlman's catalyst in methanol, and the resulting alcohol was oxidized to aldehyde **12** using Swern's procedure.[15] As with fragment **7**, the remaining stereocenter was introduced using Brown's $Ipc_2BCH_2CH{=}CH_2$ reagent prepared from (*R*)-(+)-α-pinene,[10] and the relative stereochemistry was confirmed by NMR analysis of a derivative.[16] After silylation with bis(trimethylsilyl)acetamide (BSA), the double bond in compound **13** was oxidatively cleaved with OsO_4/NMO and $NaIO_4$ to give aldehyde **14**. The synthesis of cyanohydrin acetonides **15** was completed by the addition of TMSCN to aldehyde **14** catalyzed by KCN/18-crown-6 complex,[17] followed by treatment with acetone, 2,2-DMP, and CSA. The cyanohydrin acetonides **15** were isolated as a mixture of cyanohydrin isomers in 43% overall yield from alcohol **8**.[12]

The three fragments were coupled using our alkylation and reductive decyanation method, which allows for the stereoselective construction of linear alternating polyols using a 1,3-dioxane ring as the control element.[6b] Dibromide **16** has C_2 symmetry, so only one monoalkylation product is possible. Overalkylation could be a serious problem, however, and it was avoided by using the dibromide in excess. Cyanohydrin acetonide **15** was deprotonated with $LiNEt_2$ in THF at −78 °C, 2 equiv of dibromide **16** were added, the reaction vessel was transferred to a −18 °C MeOH/ice bath, and the bath was allowed to warm to 10 °C overnight. The monoalkylated product **17** was isolated in 63% yield, and 84% of the theoretical unreacted dibromide was recovered. Bromide **17** was used as the limiting reagent in the second alkylation, and the cyanohydrin acetonide **7** was used in 2-fold excess. Deprotonation of **7** and alkylation with **17** was carried out as described for the first coupling to give the adduct **18** in 91% yield along with a small amount of recovered **7**. Reductive removal of the cyano groups is normally carried out with lithium in ammonia, but model studies suggest that the allylic ether present in **18** would also be susceptible to reduction. To avoid this difficulty dinitrile **18** was added to 10 equiv of lithium di-*tert*-butylbiphenylide (LiDBB)[18] in THF at −78 °C, and the reaction was stirred for 1 h before being quenched with MeOH. The reduced product **19** was isolated in 63% yield as a single isomer. The ^{13}C chemical shifts of acetonide methyl groups confirm the presence of three syn-chair acetonide rings (30.3, 30.3, 29.8, 20.0, 19.8, 19.0) and one anti-twist acetonide ring (24.4, 24.4), demonstrating that the two new protons are present in axial positions.[19]

Tetraacetonide **19** contains the C(12)–C(30) subunit and all 10 stereocenters of (−)-roxaticin. Compound **19** was prepared in 11 steps and 16% overall yield from alcohol **8**, and the 3-fold convergent strategy developed here lends itself to the preparation of structural analogs.

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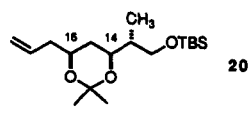
Supplementary Material Available: Experimental procedures for all new compounds (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631. (b) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858.

(14) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828. (b) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197–200.

(15) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(16) The alcohol was converted into the internal acetonide **20** by sequential treatment with (i) MeOH, CSA, (ii) TBSCl, Et_3N, and DMAP, and (iii) acetone, 2,2-DMP, CSA. Compound **20** showed acetonide methyl peaks at 19.6 and 30.0 ppm in the ^{13}C NMR, confirming the expected syn stereochemistry at C(14) and C(16). See ref 19.



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(17) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55.

(18) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.

(19) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100.