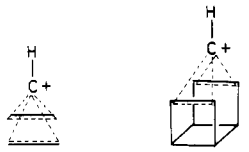
arrangement of the homocubyl cation (13).[13] Of course,



12 13

complexes like 11 become familiar structures when the isolobal analogy between CH^+ and the $Fe(CO)_3$ fragment (or CoCp, RhCp, etc.) is invoked.[14] The energy profile connecting 3 and 8 via 11 is rather symmetrical with an overall barrier of 37.6 kcal/mol. However, the highest energy structures are calculated to have a Hessian index of 2 and hence are not true transition structures. Nevertheless, a C_s trajectory via the complex, 11, is available for the Cope rearrangement of 3 requiring only a slightly greater energy than the MERP. More importantly, this trajectory requires less energy than the MERP for the Cope rearrangement of the neutral parent, 2.

An independent measure of the homoconjugative driving force was obtained by obtaining a diradical saddle point for the process 3 → 8 (Scheme IVc). This structure, 14, with a Hessian index of 1, resembles the diradical transition structure, 6,[15] but with a localized carbocation center. The corresponding activation enthalpy of 61.9 kcal/mol is also similar to that in the rearrangement of 2 → 5 (and 26.5 kcal/mol higher than that for the MERP of 3).

In summary, MNDO calculations reveal the possibility of both classical and nonclassical ion participation in the Cope rearrangement of 3.[16] We are currently examining experimentally and theoretically, with appropriately chosen systems, the role of the norbornyl skeleton and the rigid endocyclic bonds in enhancing such homoconjugative interactions.

Acknowledgment. S.L. thanks the CSIR (New Delhi) for an SRF.

(12) (a) Franke, W.; Schwarz, H.; Thies, H.; Chandrasekhar, J.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 485. (b) Franke, W.; Schwarz, H.; Thies, H.; Chandrasekhar, J.; Schleyer, P. v. R.; Hehre, W. J.; Saunders, M.; Walker, G. *Chem. Ber.* **1981**, *114*, 2808. (c) Schwarz, H.; Thies, H.; Franke, W. *Ionic Processes in the Gas Phase* **1984**, 267.

(13) Jorgensen, W. L. *J. Am. Chem. Soc.* **1977**, *99*, 4272.

(14) Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 711.

(15) Since some of the structures are diradicaloid in nature, the energy of each stationary point was recomputed with the Half Electron method including 3 × 3 C.I. As suggested by Dewar in his exhaustive studies on the Cope rearrangement,[9] the HE energy requires correction by ca. 20 kcal/mol, to compensate for overestimation of electron correlation effects. As in 4, both the RHF and the corrected HE estimates yield virtually identical barriers for all the diradicaloid pathways.

(16) As suggested by a reviewer, the relative preferences of classical and nonclassical structures may vary (probably in favor of the latter) if other theoretical methods like the MINDO/3 are used. Detailed results using this method would be presented in due course. Another reviewer has wondered whether the nonclassical participation involves a conceptually simpler bis-(or a tris-)homotropylium cation, rather than the π-complex structure proposed in this study. Comparison of geometries and charge distribution unambiguously prove that 11 is closer to the symmetrical diolefin complex[12] of CH^+ than to a homoconjugative species like the 7-norbornenyl cation.

Total Synthesis of Myxovirescin B

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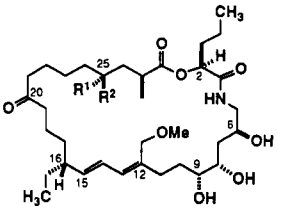
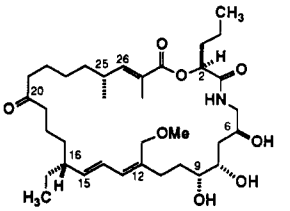
Summary: A high convergent total synthesis of optically active myxovirescin B, a 28-membered macrolactam lactone (1c), is presented. Ring closure of the macrocycle was efficiently accomplished via an intramolecular Horner–Emmons reaction of the sensitive aldehydic phosphonate 18b.

In 1982, researchers at the Gesellschaft für Biotechnologische Forschung reported the isolation of a new family of antibiotics from the myxobacterium, *Myxococcus virescin* (Mx v 48).[1] The myxovirescins, consisting of 31 structurally related macrocycles, appear to be ubiquitous among related strains of these gliding bacteria.[2,3] A postulated biological mechanism of action suggests interference with cell wall synthesis by blocking incorporation of *N*-acetylglucosamine.[1] The predominant component, myxovirescin A, was determined to be the mixture of 28-membered macrolactam–lactone diastereoisomers 1a,b by X-ray crystallography of the bisacetonide of diastereomer 1a in conjunction with degradation experiments.[2,4] Subsequently, myxovirescin B (1c) was identified as the C_{26}–C_{27} unsaturated derivative of myxovirescin A_1 (1a).[4,5] Very recently, the relative and absolute stereoassignments of the entire myxovirescin family have been resolved by Trowitzsch and co-workers.[6] Herein, we report a highly convergent synthetic pathway which has led to the first preparation of any member of these unique antibiotics with formation of optically active myxovirescin B (1c).



	R^1	R^2
1a - A_1	Me	H
1b - A_2	H	Me



1c - Myxovirescin-B

(1) Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W. *J. Antibiot.* **1982**, *35*, 1454.

(2) Trowitzsch, W.; Wray, V.; Gerth, K.; Höfle, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1340. Kunze, B.; Kuhl, W.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1985**, *38*, 1649. For biosynthetic studies: Trowitzsch, W.; Gerth, K.; Wray, V.; Höfle, G. *J. Chem. Soc., Chem. Commun.* **1983**, 1174.

(3) The megovalicins appear to be identical to the myxovirescins. Miyashiro, S.; Yamanaka, S.; Takayama, S.; Shibai, H. *J. Antibiot.* **1988**, *41*, 433.

(4) Trowitzsch, W.; Burgschulte, K.; Wray, V.; Schomburg, D.; Höfle, G. *Justus Liebigs Ann. Chem.* **1985**, 1629.

(5) Onishi, N.; Izaki, K.; Takahashi, H. *J. Antibiot.* **1984**, *37*, 13.

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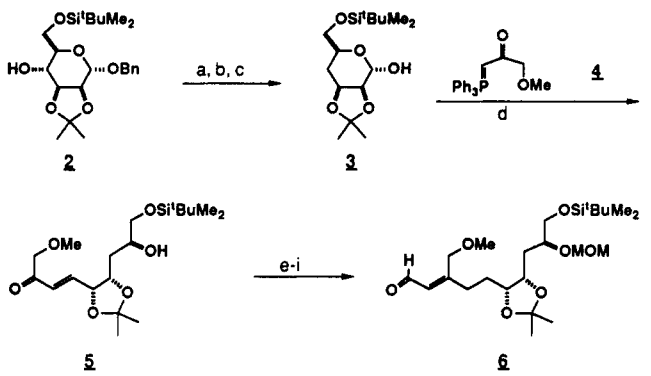
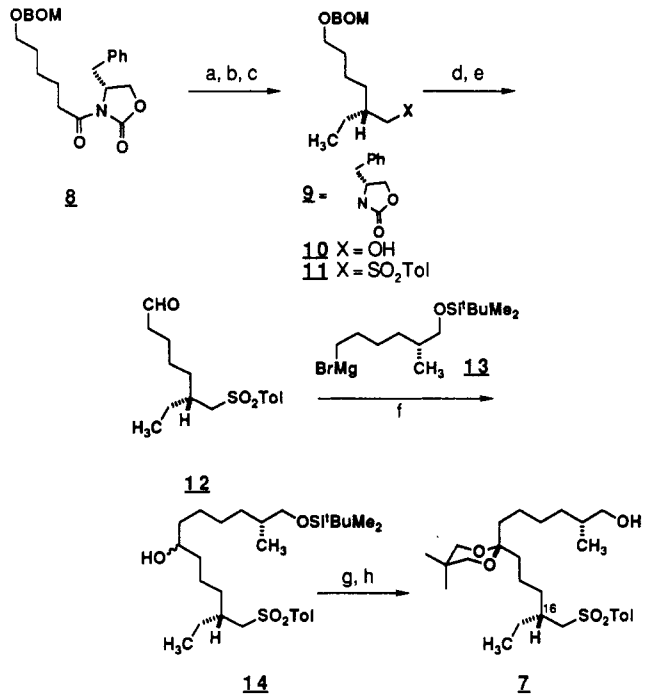
Scheme I[a]



[a] (a) $Imd_2C{=}S$; $ClCH_2CH_2Cl$; reflux (82%); (b) *n*-Bu_3SnH; toluene; reflux (87%); (c) Na; NH_3; THF (89%); (d) add **4** (3 equiv); THF; CH_3CH_2COOH (2 drops); reflux (81%); (e) H_2 (1 atm); Rh/Al_2O_3; THF (96%); (f) CH_3OCH_2Cl (3 equiv); iPr_2NEt (4 equiv); CH_2Cl_2; room temperature (88%); (g) $(EtO)_2POCH_2COOEt$ (3 equiv); NaH (3 equiv); THF; HMPA (3 equiv); add **5**; 0 → 22 °C (77%); (h) DIBAL; CH_2Cl_2; −78 °C; then MeOH; aqueous Rochelle's salt (88%); (i) excess MnO_2; CH_2Cl_2; room temperature (92%).

Our initial studies addressed preparation of the C_5–C_{14} segment (myxovirescin numbering) of the natural product with particular attention to generation of the asymmetric triol as illustrated in Scheme I. Use of a readily available carbohydrate precursor was an appealing prospect for establishing the triol with its correct absolute stereochemistry. Thus, benzyl α-D-mannopyranoside was transformed to its 2,3-acetonide,[7] and silylation of the primary hydroxyl gave **2**. Deoxygenation (at C_4 of mannose) as reported by Rasmussen[8] and subsequent debenzylation unmasked the hemiacetal **3** to serve as a substrate for Wittig elongation of the carbon chain. Standard reaction procedures using ylide **4**[9] were slow and sensitive to concentration and solvent polarity changes leading to varying amounts of a mixture of tetrahydropyrans derived from intramolecular Michael addition of the initial α,β-unsaturated product **5**. Such tandem Wittig–Michael strategies have been used as routes to *C*-glycosides, and the preexisting five-membered 2,3-acetonide was expected to facilitate ring closure.[10] However, Corey has reported the addition of benzoic acid for such cases, thereby enhancing the rate of the overall process, as well as providing for protonation of the initially formed alkoxide.[11] Application of these modifications led to enone **5** in reproducible yields of 80–85% with isolation of 5–8% of Michael products. Furthermore, no evidence for epimerization of the adjacent asymmetric center (at C_2 of **3**) was observed. The requisite trisubstituted *Z* olefin of **6** was constructed via Horner–Emmons condensation with the stabilized anion of triethyl phosphonoacetate, affording a separable mixture of unsaturated esters **6ab** (91% as 5:1 ratio of *Z*:*E* isomers). Proton and carbon NMR spectra clearly distinguished the *Z* and *E* olefin geometries of each pure isomer. Overall the desired aldehyde **6** was obtained in 27% yield from **2**.

Scheme II[a]



[a] (a) $NaN(TMS)_2$; THF; EtOTf (5 equiv); −78 → −30 °C (65%); (b) $LiAlH_4$; Et_2O; 0 °C (84%); (c) I_2; Ph_3P; imidazole; CH_2Cl_2; 0 → room temperature (90%); then $NaSO_2Tol$; DMF; room temperature (85%); (d) H_2 (1 atm); Pd-black; MeOH; concentrated HCl (2 drops) (97%); (e) $(COCl)_2$; DMSO; NEt_3; −78 °C → room temperature (85%); (f) add **13** in ether; 0 °C (83%); (g) PCC on Al_2O_3; CH_2Cl_2 (97%); (h) 2,2-dimethyl-1,3-propanediol; PhH; TsOH (catalytic amount); 80 °C (86%).

The western portion (C_{15}–C_{26}) of myxovirescin B was readily assembled as the optically active sulfone **7** as summarized in Scheme II. The key asymmetric center at C_{16} was established using Evans alkylation methodology provided from 4(*R*)-benzyl-2-oxazolidinone.[12] Optimized alkylations required stirring with excess ethyl triflate (5 equiv) at −30 °C for 10 h, yielding 65–70% of **9** as a single isomer with approximately 15–20% recovery of starting **8**.[13] Reductive removal of the chiral auxiliary at 0 °C gave the optically active alcohol **10**[14] for efficient conversion to the corresponding sulfone **11**. Nucleophilic addition of the Grignard reagent **13**[15] incorporated the remaining carbons of the western segment **7**.

The convergence of our synthetic pathway and critical steps leading to formation of the 28-membered macrocycle of myxovirescin B are summarized in Scheme III. The

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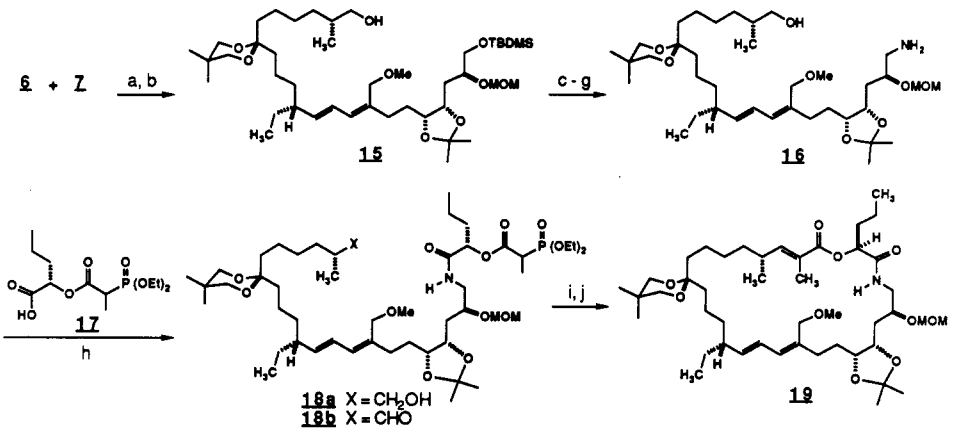
(12) For preparation of **8**: Protection of methyl 6-hydroxyhexanoate (Bosone E.; Farina, D.; Guazzi, G.; Innocenti, S.; Marotta, V. *Synthesis* **1983**, 942) with (benzyloxy)methyl chloride (iPr_2NEt; CH_2Cl_2; room temperature), ester saponification (LiOH; aqueous MeOH; THF), and treatment with pivaloyl chloride (THF; Et_3N; 0 °C) was followed by condensation with 3-lithio-4(*R*)-benzyl-2-oxazolidinone (Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757).

(13) Alkylations using ethyl iodide gave 28% yield of **9**. The two (C_{16}) diastereomers of **9** were prepared via condensation of 2-lithio-4(*R*)-benzyl-2-oxazolidinone with the mixed anhydride from racemic 6-(((benzyloxy)methylene)oxy)-2-ethylhexanoic acid. The resulting isomers **9a,b** were chromatographically separable and gave distinctive ^{13}C NMR spectra.

(14) Mosher ester analysis of alcohol **10** gave further evidence of a single C_{16} stereochemistry suggesting an isomeric ratio >98:2.

(15) The Grignard reagent **13** was produced from (+)-methyl 3-hydroxy-2(*S*)-methylpropionate. See reference 5 of: Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. Complete details will be provided in the full account of this work.

Scheme III[a]



[a] (a) *n*-BuLi (8 equiv); THF; add 7 (4 equiv); −78 °C for 30 min; then 6 (1 equiv); (b) Na(Hg) 6%; THF/MeOH (2:1 ratio); KH_2PO_4 (20 equiv); 22 °C (79% for two steps); (c) Ac_2O; Et_3N; CH_2Cl_2; DMAP (catalytic amount) (98%); (d) *n*-Bu_4NF; THF (94%); (e) MsCl; Et_3N; CH_2Cl_2; DMAP; then LiN_3; DMF at 60 °C (95%); (f) K_2CO_3; MeOH; 22 °C (96%); (g) Ph_3P (3 equiv); THF; reflux; then NH_4OH (91%); (h) 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate; CH_2Cl_2; 0 °C → 22 °C (92%); (i) $(COCl)_2$; DMSO; CH_2Cl_2; then Et_3N at −78 °C → room temperature (92%); (j) DBU (2 equiv); CH_3CN; LiCl (50 equiv); 6×10^{-4} M in **18b** at 22 °C (78%).

Julia–Lythgoe reductive coupling of components **6** and **7** proceeded smoothly (within 30 min) without the usual derivatization of intermediate β-sulfonyl alcohols prior to treatment with freshly prepared sodium amalgum in a buffered medium.[16] The crude product **15** was isolated as a mixture of *E*/*Z* C_{14}–C_{15} isomers (ratio 90:10). Transformation to the primary amine **16** was accomplished via a nucleophilic displacement of the C_5 mesylate with lithium azide followed by mild, selective reduction of the azido function with triphenylphosphine and basic hydrolysis of the intermediate iminophosphorane.[17] Carbodiimide-mediated coupling of the amino alcohol **16** with carboxylic acid **17** exclusively gave N-acylation. Component **17** was itself produced by esterification (DCC; CH_2Cl_2; DMAP; room temperature (86%)) of diethyl 2-phosphonopropionic acid with benzyl 2(*S*)-hydroxypentanoate followed by catalytic hydrogenolysis of the benzyl ester (H_2; 10% Pd–C; THF (100%)).[18] Preliminary oxidation of alcohol **18a** and intramolecular ring closure of **18b** by a Horner–Emmons procedure using the Masamune–Roush modification[19] afforded an excellent yield of the α,β-unsaturated macrolactone **19** as a mixture of C_{26}–C_{27} olefin geometries (*E*/*Z* ratio 7:1). Reactions of the corresponding diisopropyl phosphonate of **18b** proved to be sluggish, and resulted in complete epimerization of C_{25} stereochemistry. Quenched reactions showed that recovered starting aldehyde **18b** had undergone considerably more epimerization at C_{25} than that observed by resubmission of pure product **19** to cyclization conditions. Substitution of Hünig's base for DBU gave no reaction. While reduced quantities of LiCl (5 equiv) and DBU (5 equiv) eliminated problems of C_{25} isomerization, these attempts surprisingly gave only the dimeric product of intermolecular condensation.[20] Our optimized procedure required slow addition of DBU (2 equiv) in CH_3CN via a syringe pump over a 2-h period to a solution of LiCl (50 equiv) and **18b** (6×10^{-4} M) in acetonitrile, yielding an efficient ring closure without epimerization. Preparative HPLC chromatography (elution with CH_3CN/PhH, ratio 1:4) afforded the pure (*E*)-α,β-unsaturated macrolactone **19**. Finally, all protecting units were removed upon acid hydrolysis at 60 °C (THF; H_2O; CH_3OH (5 drops); $HClO_4$ (2 drops); 22 → 60 °C; 1 h (70%)) providing crystalline myxovirescin B (**1c**). Identification of our synthetic material was verified by direct comparison with a sample of the natural product as kindly supplied by Wolfram Trowitzsch-Kienast.[21]

Acknowledgment. We gratefully acknowledge financial assistance provided by the National Institutes of Health (GM-41560) and the National Science Foundation (CHE86-18955).

Supplementary Material Available: Spectral and analytical data for key substances and synthetic myxovirescin B (10 pages). Ordering information is given on any current masthead page.

(16) Reductions carried out in nonprotic solvent and without added buffers gave only sulfone **7** with evidence of reversible addition of the initial β-sulfonyl alcohols. For a review: Kocienski, P. J. *Chem. Ind. Lett.* **1981**, 548.

(17) Mungall, W. S.; Greene, G. L.; Heavner, G. A.; Letsinger, R. L. *J. Org. Chem.* **1975**, *40*, 1659. Gololobov, Y. G.; Zhmurova, I. N.; Kasulchin, L. F. *Tetrahedron* **1981**, *37*, 437.

(18) Benzyl 2(*S*)-hydroxypentanoate was obtained from diazoatization of L-norvaline (Winitz, M.; Block-Frankenthal, L.; Izumiya, V.; Birnbaum, S. M.; Baker, C. B.; Greenstein, J. P. *J. Am. Chem. Soc.* **1956**, *78*, 2423), and esterification with benzyl bromide (Et_3N; EtOAc; reflux; 60% for two steps). Mosher ester analysis of the product indicated 94% ee.

(19) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(20) Use of kinetic bases were also examined. Treatment of **18b** with NaH in THF (1×10^{-3} M concentration) at 22 °C gave cyclization without epimerization in 70% yield as a 60:40 ratio of *E*/*Z* **19**. Deprotonation with lithium hexamethyldisilazide (1 equiv) in THF (1×10^{-3} M) led solely to dimeric product formation.

(21) Our material was indistinguishable from a pure sample of myxovirescin B generously supplied to us by Wolfram Trowitzsch-Kienast, Gesellschaft für Biotechnologische Forschung, Mascheroder Weg 1, D-3300, Braunschweig, West Germany.