(>98% ^{1}H NMR).[13] The stereochemistry indicated in eq 1 is assigned by analogy with a structurally characterized neutral zirconium ketene complex formed in a similar fashion[9] and is attributed to the steric requirements of **3**. Benzyl bromide and trimethylsilyl chloride react similarly with **2a**.[14] Attempts at an aldol-type reaction of **2a** with benzaldehyde led to complex mixtures of products.

Metallaenolate (ketene) anion **2a** has been found to be of general utility in the preparation of new homo- and heteronuclear bimetallic ketene complexes of interest as models of intermediates implicated in carbon–carbon bond formation in surface-catalyzed carbon monoxide reductions.[15] Reaction of **2a**·Et_2O with zirconocene halide **4a** (eq 2) proceeds rapidly upon dissolution in

4a, L = Cp; M = Zr; X = CH_3 **5a**, Y = Z = CH_3; M = Zr
b, L = $P(CH_3)_3$; M = Pt; X = CH_3 **b**, Y = Z = CH_3; M = Pt

THF/Et_2O at −20 °C, and the binuclear ketene complex **5a** is isolated in ca. 50% yield.[16-18] The assigned structure differs from the "bridging acyl" type structures of Ru[8a] and Os[8b] μ,η^2-$OCCH_2$-*C,C* complexes, a consequence of the oxophilicity of zirconium.

Platinum halides of the type *cis*-L_2PtXCl, such as **4b** (L = $P(CH_3)_3$, X = CH_3), react cleanly with **2a**·2THF in benzene at room temperature to afford heterobinuclear bridging ketene complexes (eq 2).[19] The μ-η^2-$OCCH_2$ structure indicated in eq 2 is supported by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopic data.[20] The inequivalence of the phosphine ligands and the different J_{HP} and J_{PPt} values establish cis orientation about Pt in **5b**.

The metallaenolate anions **2** are versatile reagents in organometallic synthesis, particularly for formation of binuclear complexes of relevance to carbon monoxide reduction systems. The reactivity of these new ketene species, including use of complexes such as **2** and **5** in stereospecific organic transformations, is presently being explored.

Acknowledgment. We acknowledge the financial support of the Department of Energy.

Supplementary Material Available: Tables of atomic coordinations, bond angles, bond distances, structure factors, and thermal parameters for **2a**·2THF (18 pages). Ordering information is given on any current masthead page.

(13) For **2a**: ^{1}H NMR (THF-d_8) δ −0.68 (s, 3 H), 3.64 (d, J = 2 Hz,1 H), 4.55 (d, J = 2 Hz, 1 H), 5.43 (s, 10 H). **2b**: ^{1}H NMR (THF-d_8) δ −0.68 (s, 3 H), 1.82 (d, 3 H, J = 6 Hz), 5.07 (q, 1 H, J = 6 Hz), 5.45 (s, 10 H). **2c**: ^{1}H NMR (THF-d_8) δ −0.77 (s, 3 H), 1.68 (s, 3 H), 1.83 (s, 3 H), 5.34 (s, 10 H). By modification of reaction conditions it is possible to generate a minor isomer of **2b**.[14]

(14) Ho, S. C. H.; Grubbs, R. H., unpublished results.

(15) (a) Blyholder, G.; Emmet, P. H. *J. Phys. Chem.* **1960**, *64*, 470 and references therein. (b) Wolczanski, P. T.; Bercaw, J. E. *Acc. Chem. Res.* **1980**, *13*, 121.

(16) For **5a**: ^{1}H NMR (C_6D_6) δ −0.17 (s, 3 H), 0.43 (s, 3 H), 4.23 (s, 1 H), 4.61 (s, 1 H), 5.65 (s, 10 H), 5.82 (s, 10 H); ^{13}C NMR (C_6D_6) δ 18.8 (q, $^1J_{CH}$ = 117 Hz), 33.0 (q, $^1J_{CH}$ = 119 Hz), 92.7 (dd, $^1J_{CH}$ = 148, 159 Hz), 107.1 (dm, $^1J_{CH}$ = 172 Hz), 113.1 (dm, $^1J_{CH}$ = 172 Hz), 208.9 (pseudotriplet, $^2J_{CH}$ = 9 Hz); IR (KBr) 1538, 1594 cm^{-1} ($\nu_{C=C}$). Anal. $C_{24}H_{28}OZr_2$ (C, H).

(17) The inequivalence of the two zirconium centers of **5a** in the ^{1}H NMR at room temperature stands in contrast with the formaldehyde complex $(Cp_2ZrCl)_2(\mu$-$OCH_2)$ (Gambarotta, S.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Am. Chem. Soc.* **1983**, *105*, 1690) and related complexes (Erker, G.; Kropp, K. *Chem. Ber.* **1982**, *115*, 2437). This might be due to the sp^2 hybridization at the oxygen-bound carbon, which inhibits formal dative Zr–O interaction. Examination at high temperature is not possible because **5a** undergoes bimolecular decomposition to $(Cp_2Zr(OCCH_2))_n$ (identified by comparison with an authentic sample[14]) and $Cp_2Zr(CH_3)_2$ (k = 1.1 × 10^{-2} L mol^{-1} s^{-1}, 52 °C).

(18) Binuclear zirconium ketenes with Y = OCH_3, Z = CH_3 and Y = CH_3, Z = Cl have also been prepared.

(19) PtL_2XCl (L = $P(CH_3)_2Ph$, PCH_3Ph_2; X = CH_3, Cl) react to give similar ketene-bridge complexes.

(20) For **5b**: ^{1}H NMR (C_6D_6) δ 6.08 (s, 10 H), 5.06 (ddd, J_{HH} = 2, J_{HP} = 13, 3, J_{HPt} = 90 Hz, 1 H), 4.00 (ddd, J_{HH} = 2, J_{HP} = 3, J_{HPt} = 32 Hz, 1, H), 1.20 (d, J_{HP} = 8.5, J_{HPt} = 21.7 Hz, 9 H), 1.04 (dd, J_{HP} = 9.6, 17.5, J_{HPt} = 69.6 Hz, 3 H), 0.93 (d, J_{HP} = 7.8, J_{HPt} = 19.4 Hz, 9 H), 0.39 (s, 3 H); ^{13}C NMR (C_6D_6) δ 202.1, 152.9, 110.3, 36.4, 17.3, 15.9, 13.9; ^{31}P NMR (C_6D_6) δ −29.3 (d, J_{PP} = 12.1, J_{PPt} = 1354 Hz), −25.0 (d, J_{PP} = 12.2, J_{PPt} = 1578 Hz).

Stereocontrol of Michael Hydride Reduction by a Remote Hydroxyl Group. A Strategy for Stereorational Total Synthesis of Spatane Diterpenes

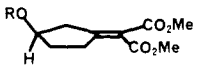
Robert G. Salomon,* Navzer D. Sachinvala, Swadesh R. Raychaudhuri, and Donald B. Miller

Department of Chemistry
Case Western Reserve University
Cleveland, Ohio 44106

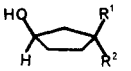
Received September 23, 1983
Revised Manuscript Received February 3, 1984

The remarkable biological activities of spatane diterpenes,[1] especially spatol (**1**),[2] make them attractive targets for synthesis. Our strategy for total synthesis of spatanes (Scheme I) envisions completion of the C_{20} skeleton from C_{15} tricyclodecane precursors such as **2a** or **2c**. The requisite stereochemistry at C-7 is assured if some derivative of the C-5 hydroxyl substituent directs syn Michael addition of hydride to C-7 in an alkylidene malonic ester as in **4** → **3**. The correct relative configurations of the C-5 hydroxyl and B-ring stereocenters is assured by exo stereoselectivity anticipated[3] in the photocycloaddition of **7**[4] with norbornenes. We now report the *first* total synthesis of a spatane diterpene, (±)-spata-13,17-dien-5-ol (**25**), and show that hydride delivery during reduction of alkylidene malonates like **4** can be directed ether syn or anti by a homoallylic hydroxyl group or the derived MEM ether, respectively.

Considering the obvious synthetic utility of stereodirected Michael additions, there are remarkably few examples of such processes. To explore the efficacy of various homoallylic substituents as stereodirecting groups, MEM ether **9a** was reduced



9a, R = MEM
9b, R = H



10t, R^1 = H, R^2 = $CH(CO_2Me)_2$
10c, R^2 = $CH(CO_2Me)_2$, R^2 = H

with $NaBH_4$ in ethanol followed by removal of the MEM protecting group.[5] A 1:5 mixture of the trans and cis hydroxy malonic esters **10t** and **10c** was obtained. Thus the MEM ether group functions as a bulky steric hinderance to syn approach of the hydride. This contrasts with the syn stereodirecting effect of an allylic MEM ether group which served as a chelating ligand during "heteroconjugate addition" of MeLi.[6] Most significantly, the stereochemical outcome was reversed by first removing the MEM protecting group. Treatment of **9b** with $NaBH_4$ in ethanol produced a 1.0:0.67 mixture of **10t** and **10c**. Further improvement in the product ratio to 1.0:0.37 was achieved by using THF as solvent. The solvent effect can be understood in terms of activation

(1) Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233.

(2) (a) Spatol inhibits cell division in human T242 Melanoma and 224C astrocytoma neoplastic cell lines: Gerwick, W. H.; Fenical, W.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7991. (b) Spatol's antimitotic activity apparently results from inhibition of microtubule assembly: Jacobs, R. S.; White, S.; Wilson, L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1981**, *40*, 26.

(3) Hara, M.; Odaira, Y.; Tsutsumi, S. *Tetrahedron* **1966**, *33*, 95.

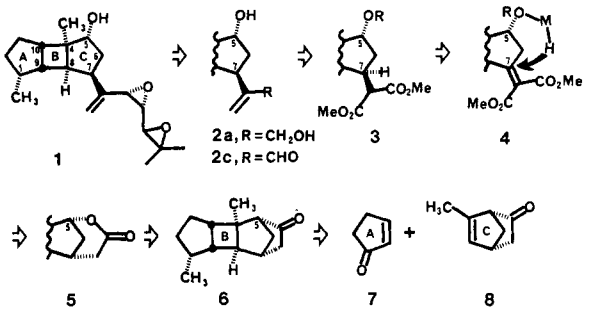
(4) White, J. D.; Gupta, D. N. *J. Am. Chem. Soc.* **1968**, *90*, 6171.

(5) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

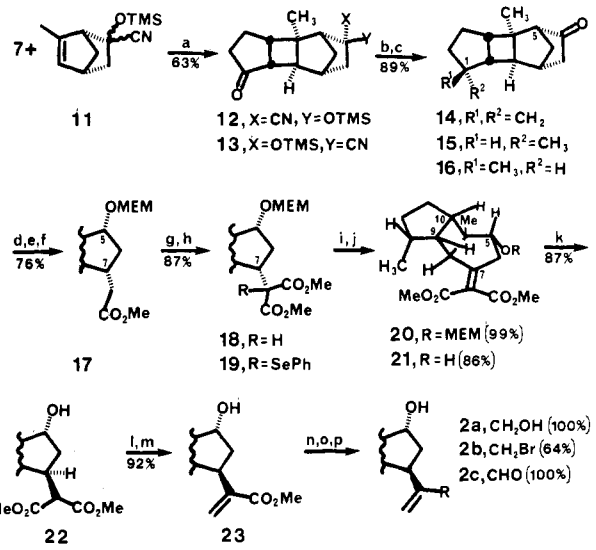
(6) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465.

0002-7863/84/1506-2211$01.50/0

Scheme I



Scheme II[a]



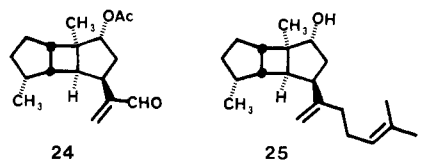
[a] Reagents and conditions: (a) $h\nu$/uranium glass filter/hexane; (b) Ph_3PCH_2 (2.3 equiv)/THF then add H_2O/20 °C, 3 h; (c) H_2/Pt_2O; (d) CH_3CO_3H/CH_3COOH; (e) KOH/H_2O/MeOH then HCl then CH_2N_2; (f) MEMCl/i-Pr_2NEt/CH_2Cl_2; (g) LDA then CO_2 then HCl then CH_2N_2; (h) NaH/THF then add PhSeBr; (i) H_2O_2/CH_2Cl_2; (j) $TiCl_4/CH_2Cl_2$; (k) $NaBH_4$/THF; (l) KOH (1.0 equiv)/EtOH/H_2O then HCl; (m) $CH_2O/H_2O/Et_2NH$/NaOAc/HOAc; (n) i-Bu_2AlH/toluene; (o) $Ph_3P/CBr_4/CH_3CN$; (p) MnO_2/CH_2Cl_2.

of borohydrides by *B*-alkoxy groups.[7] In ethanol, ethoxyborohydrides react intermolecularly, whereas in THF, pseudointramolecular reaction is favored for alkoxyborohydride derivatives of the homoallylic hydroxyl substituent.[8]

Our synthesis of the key intermediates **2a** and **2c** is outlined in Scheme II.[9] Trimethylsilyl cyanohydrin **11** was obtained quantitatively from **8**[10] by reaction with trimethylsilanecarbonitrile.[11] Although **11** was an epimeric mixture, this choice for masking the carbonyl proved remarkably fortunate (vide infra). Photocycloaddition of **7** with **11** in hexane solution produced an awesome mixture of products. Serendipitously, the required epimers **12** and **13** were readily isolated by crystallization. Thus, **13** crystallized from the photoreaction mixture together with dimers of **7** from which it was readily separated by trituration with boiling hot hexane leaving behind pure dimer. Pure **13** (mp 109–111 °C)[12] was then obtained in 51% yield based on **11** by passage of the partially purified material through a column of silica gel with ethyl acetate–hexane. Column chromatography of the hexane-soluble photoproduct afforded a fraction from which nearly pure **12** crystallized together with a little **13**. This mixture is suitable for Wittig olefination (vide infra) so that the combined isolated yield of **12** plus **13** exceeds 60%. The epimeric relationship between **12** and **13** was proven by production of the same methylidene ketone **14** upon reaction with methylenetriphenylphosphorane followed by hydrolysis. The **13** → **14** conversion was performed as a one-pot procedure, which afforded pure **14** (mp 52–53 °C) in 89% overall yield. Thus, the cyanohydrin silyl ether is sufficiently robust to survive UV irradiation and Wittig olefination, but is readily converted to a carbonyl group by aqueous base.

Catalytic hydrogenation of **14** was expected to deliver hydrogen preferentially from the less congested exo face of the C=C bond to give the *endo*-methyl epimer **15**. With PtO_2 as catalyst precursor, **15** was favored over the *exo*-methyl epimer **16** by about 9:1. The seemingly tedious separation of **15** and **16** is in fact trivial. Thus, pure **15** (mp 53–55 °C) was readily isolated from the mixture by crystallization from pentane at −78 °C. Baeyer–Villiger oxidation of **15** then introduced the C-5 oxygen substituent stereospecifically. The carbon skeleton was completed by carboxylation of ester **17**. Inversion of the configuration at C-7 in diester **18** was then initiated by selenation to give **19**, oxidative dehydroselenation of which afforded the alkylidenemalonate **20**. Removal of the MEM protecting group provided **21**.

The crucial stereocontrolled Michael reduction was then examined. Reduction of the MEM ether **20** with $NaBH_4$ in ethanol followed by removal of the MEM protecting group afforded a 1:2 mixture of the desired **22** and its C-7 epimer, respectively. As with the model **9**, the MEM ether substituent in **20** sterically hinders the desired syn delivery of hydride. In contrast with **9**, anti delivery of hydride is also hindered for **20** by the hydrogens at positions 9 and 10 resulting in nonstereoselective reduction. Most gratifyingly, the combination of this steric hinderance to anti hydride delivery with the syn stereodirecting influence of a homoallylic hydroxyl substituent results in highly stereoselective reduction of hydroxyalkylidenemalonate **21**. Thus, **21** afforded **22** with no trace of the C-7 epimer upon treatment with $NaBH_4$ in THF. Selective monosaponification of **22** was readily achieved, and Mannich condensation with subsequent decarboxylative elimination generated α,β-unsaturated ester **23** in a one-pot reaction from the monoacid.[13] Reduction of ester **23** with diisobutylaluminum hydride gives the target allylic alcohol **2a** (mp 97–98 °C) quantitatively. The diol **2a** was selectively converted to a monobromide **2b** (mp 72–73 °C) upon reaction with triphenylphosphine and carbon tetrabromide.[14] Selective oxidation of **2a** with MnO_2 provided the target aldehyde **2c** (mp 89–91 °C). For comparison with a degradation product from spatol, **2c** was acetylated. The ^1H NMR spectrum of racemic acetate **24** (mp



68–71 °C) is identical with that of (+)-**24** derived from spatol.[1] The *first* total synthesis of (±)-spata-13,17-diene-5-ol (**25**) was completed by copper(I) iodide catalyzed coupling of prenylmagnesium chloride[15] with the allylic bromide **2b**. The ^1H NMR

(7) (a) Brown, H. C.; Mead, E. J.; Shoaf, C. J. *J. Am. Chem. Soc.* **1956**, *78*, 3616. (b) Rickborn, B.; Wuesthoff, M. T. *Ibid.* **1970**, *92*, 6894.

(8) Analogous stereodirected reactions involving metal hydride derivatives of allylic alkoxides were postulated previously: (a) Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, *100*, 1940. (b) Lansbury, P. T.; Vacca, J. P. *Tetrahedron Lett.* **1982**, *23*, 2623.

(9) All new compounds were thoroughly characterized spectroscopically and by elemental analysis or measurement of the exact mass of the parent ion in the high-resolution mass spectrum.

(10) Brown, H. C.; Peters, E. N.; Ravindranathan, J. *J. Am. Chem. Soc.* **1975**, *97*, 7449.

(11) (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56; (b) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929–4932.

(12) Evidence for the structure assigned to **13** is provided by extensive 200 MHz ^1H and 50 MHz ^{13}C–^1H two-dimensional J spectroscopy and ^{13}C–^1H two-dimensional shift correlation spectroscopy: Rinaldi, P. L.; Salomon, R. G. *J. Org. Chem.* **1983**, *48*, 3182.

(13) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489.

(14) Nasipuri, D.; Raychaudhuri, S. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 262.

(15) (a) Derguini-Boumechal, F.; Lorne, R.; Linstrumelle, G. *Tetrahedron Lett.* **1977**, 1181. (b) Kwart, H.; Miller, R. K. *J. Am. Chem. Soc.* **1954**, *76*, 5403.

spectrum of racemic **25** is identical with that of (+)-**25** isolated from *Stoechospermum marginatum*.[1]

Acknowledgment. This research was assisted financially by Grant CHE8205122 from the National Science Foundation and sabbatical year support of R.G.S. by Case Western Reserve University for which we are grateful. We thank Professor W. Fenical for ^{1}H NMR spectra of authentic (+)-**24** and (+)-**25**.

Biosynthesis of Cationomycin: Direct and Indirect Incorporation of [^{13}C]Acetate and Application of Homoscalar Correlated 2-D ^{13}C NMR and Double Quantum Coherence

Makoto Ubukata, Jun Uzawa, and Kiyoshi Isono*

The Institute of Physical and Chemical Research
Wako-shi, Saitama 351, Japan

Received October 31, 1983

Cationomycin is a polyether ionophore antibiotic produced by a rare actinomycete, *Actinomadura azurea*.[1,2] It is structurally unique, having an aromatic acyl side chain.[3] It binds selectively monovalent cations and is under development as a controlling agent for chicken coccidiosis because of its remarkable activity and relative low toxicity.[4] As part of the research directed toward chemical and biological modification of this interesting molecule, we report herein the biosynthesis of cationomycin, including the unambiguous assignment of the ^{13}C NMR of cationomycin labeled with [1,2-^{13}C]acetate by double quantum coherence[5] and homoscalar correlated 2-D ^{13}C NMR (COSY),[6] and a reasonable explanation for randomization of the [2-^{13}C]acetate.

An assignment of ^{13}C NMR of cationomycin[7] was based on that of structurally related laidlomycin,[8] INEPT ^{13}C NMR analysis,[9] and calculation with substituent parameters.[10] [1-^{13}C]Acetate, [1-^{13}C]propionate, [3-^{13}C]propionate, and [methyl-^{13}C]-L-methionine were incorporated as expected.[11] However,

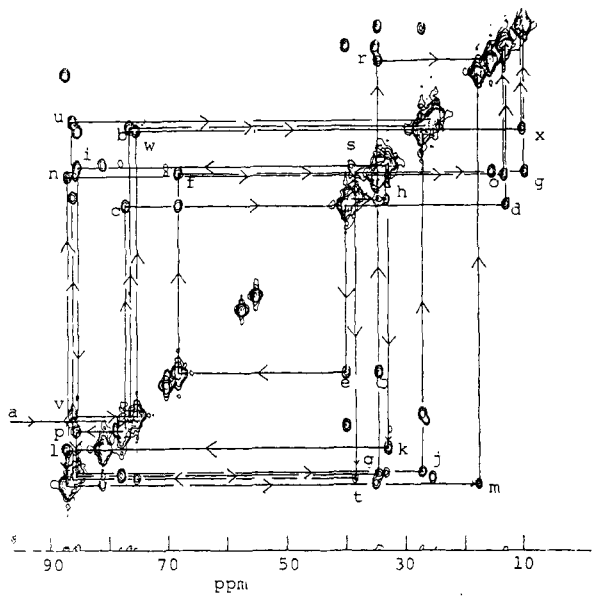
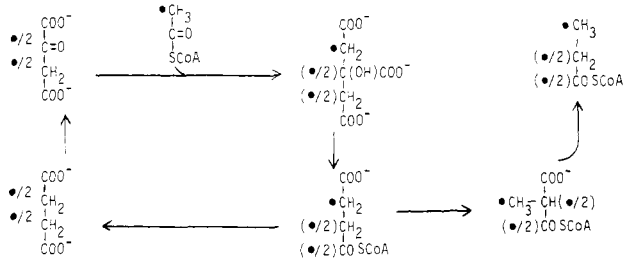


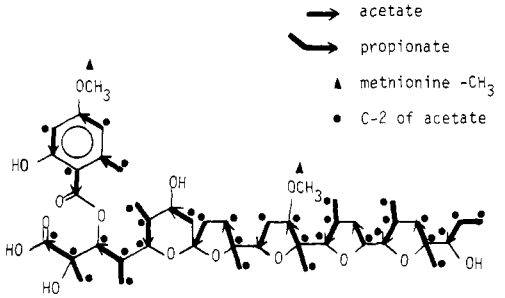
Figure 1. Homoscalar correlated 2-D ^{13}C NMR of cationomycin labeled with [2-^{13}C]acetate. The spectrum was obtained by COSY sequence[12] on ^{13}C nucleus with ^{1}H decoupling through the experiment at 100 MHz using Jeol GX 400 (acquisition time ca. 40 h, dimension of matrix 256 × 1024, dimension of transformation 512 × 1024, amount of the compound used ca. 20 mg). (a) Correlation of C-1 with C-2, (b) C-2 with 2-Me, (c) C-3 with C-4, (d) C-4 with 4-Me, (e) C-4 with C-5, (f) C-5 with C-6 (g) C-6 with 6-Me, (h) C-10 with C-11, (i) C-11 with C-12, (j) C-12 with 12-Me, (k) C-14 with C-15, (l) C-15 with C-16, (m) C-16 with 16-Me, (n) C-17 with C-18, (o) C-18 with 18-Me, (p) C-20 with C-21, (q) C-21 with C-22, (r) C-22 with 22-Me, (s) C-22 with C-23, (t) C-23 with C-24, (u) C-24 with 24-Me, (v) C-24 with C-25, (w) C-25 with C-26, (x) C-26 with C-27.

Scheme I. Pathway for Propionate from [2-^{13}C]Acetate through the Krebs Cycle[a]



[a] Parentheses show the labeling pattern for the second cycle.

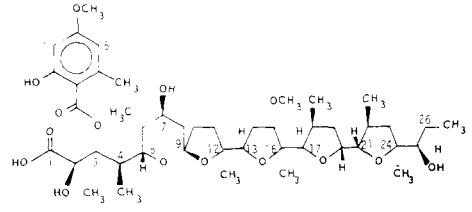
Scheme II. Biogenesis of Cationomycin



feeding of [2-^{13}C]acetate resulted in considerable randomization. In the ^{13}C NMR spectrum of cationomycin labeled with [1,2-^{13}C]acetate, the application of double quantum coherence and homoscalar 2-D ^{13}C NMR revealed eight pairs of ^{13}C–^{13}C coupling, $J_{1'\text{-}CO,1'}$ (= 76 Hz), $J_{2',3'}$ (= 70.8 Hz), $J_{4',5'}$ (= 65.8 Hz), $J_{6',6'\text{-Me}}$ (= 42.7 Hz), $J_{7,8}$ (= 37.8 Hz), $J_{9,10}$ (= 41.5 Hz), $J_{13,14}$ (= 36.6 Hz), and $J_{19,20}$ (= 36.6 Hz).

In the case of [2-^{13}C]acetate, the carbons that should be derived from C-1, C-2, and C-3 of propionate were also enriched. Homoscalar correlated 2-D ^{13}C NMR and double quantum coherence

(1) Nakamura, G.; Kobayashi, K.; Sakurai, T.; Isono, K. *J. Antibiot.* **1981**, *34*, 1513.
(2) Nakamura, G.; Isono, K. *J. Antibiot.* **1983**, *36*, 1468.
(3) Sakurai, T.; Kobayashi, K.; Nakamura, G.; Isono, K. *Acta Crystallogr., Sect. B* **1982**, *B38*, 2471.
(4) Nakamura, G.; Kobayashi, K.; Sakurai, T.; Isono, K. *Antimicrob. Agents Chemother.* **1982**, *22*, no. 170.
(5) (a) Bax, A.; Freeman, R.; Kempsell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4849. (b) Mackenzie, N. E.; Baxter, R. L.; Scott, A. I.; Fagerness, P. E. *J. Chem. Soc., Chem. Commun.* **1982**, 145. (c) Bacher, A.; LeVan, Q.; Bühler, M. *J. Am. Chem. Soc.* **1982**, *104*, 3754.
(6) Though 2-D INADEQUATE experiments have generally been applied to assignment of double-labeled compounds,[5] satisfactory data were obtained by homoscalar correlated 2-D ^{13}C NMR (COSY) experiment in this case.
(7) The numbering was conventionally adopted as follows:



(8) Seto, H.; Ōtake, N. *Heterocycles* **1982**, *17*, 555.
(9) (a) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101* 760. (b) Doddrell, D. M.; Pegg, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6388. INEPT ^{13}C NMR spectra were obtained at 25 MHz using Jeol FX 100.
(10) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: London, 1976.
(11) The experiment was done by feeding ^{13}C-labeled compounds (100–400 mg, 90% enriched) in two portions at 36 and 48 h after inoculation to a shaking culture of *A. azurea* in an organic medium (350 mL). After a total 144-h fermentation, cationomycin was isolated as described before,[1] average yield ca. 20 mg.
(12) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *42*, 164.

0002-7863/84/1506-2213$01.50/0