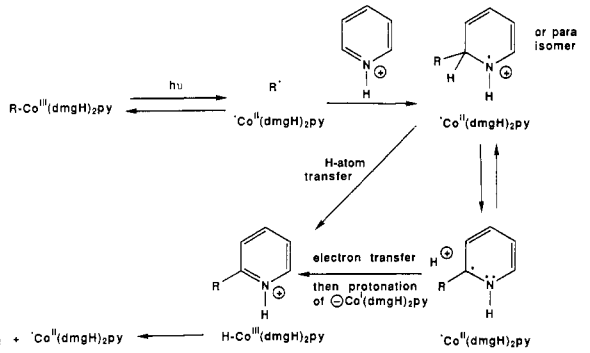
Scheme I



venger, diverting the reaction flux into the nonchain mechanism via the H-atom transfer and/or deprotonation–electron-transfer pathways of Scheme I. In contrast, the radical chain mechanism can work for organomercurials[12] because (1) it is much easier to propagate the chain via one electron transfer to alkylmercuric halides ($E_{1/2}$ = −0.4 to −0.6 V vs SCE)[15] compared to RCo^{III}(dmgH)$_2$py ($E_{1/2}$ = −1.9 to −2.2 V vs SCE)[13] and (2) in the organomercurial chemistry a stable organometallic radical such as ·Co^{II}(dmgH)$_2$py is not available to act as a chain-terminating radical scavenger.

In summary, the results presented here demonstrate that cobaloxime-mediated radical alkyl–heteroaromatic cross-coupling is feasible. The reactions proceed under mild conditions and are compatible with common organic functional groups and hydroxylic solvents. To our knowledge, the reactions reported here are the first examples of cobalt-mediated radical alkyl–heteroaromatic cross-coupling.

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Supplementary Material Available: Experimental procedures along with NMR, IR, and MS data as summarized in footnote 6 (9 pages). Ordering information is given on any current masthead page.

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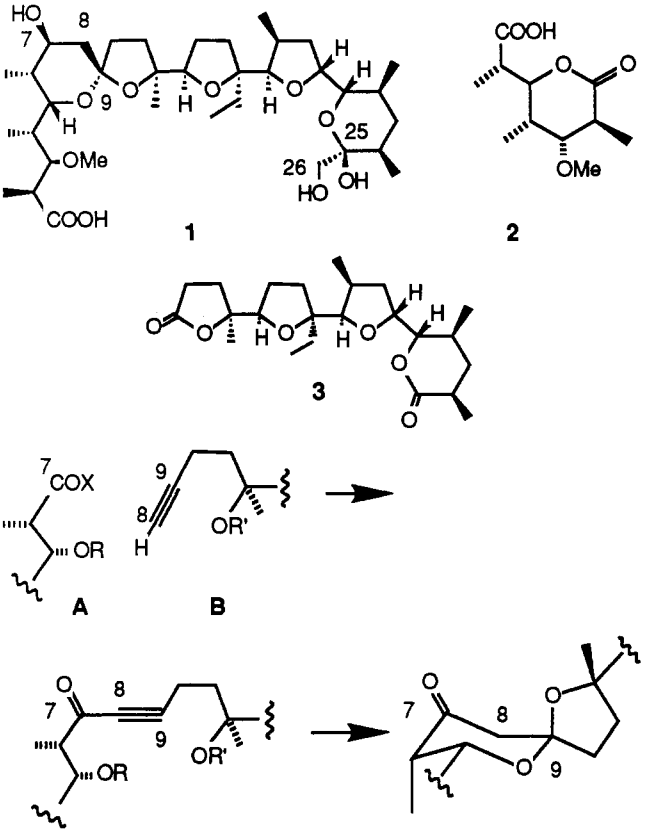
Synthesis of Monensin. Reconstruction from Degradation Products

Summary: Monensin is synthesized by a relay approach in 19% yield from two known chromic acid degradation products. The two fragments are joined by addition of a magnesium acetylide to an activated ester, and the C7 stereochemistry is set by stereoselective reduction.

Sir: In the original syntheses[1] of the polyether antibiotic monensin A[2] (1), an aldol reaction was used to join precursor fragments by formation of the C_7–C_8 bond with creation of the C_7 stereocenter. Many of the syntheses of the other polyether ionophores have also followed this route although not without encountering occasional difficulties. In our previous synthesis, for example, we were unable to obtain high chemical yields of the C_7–C_8 aldol during the coupling and simultaneously control the C_7 carbinol stereochemistry. As an alternative approach, we have investigated a construction that avoids the problematic aldol methodology and separates the C_7–C_8 bond formation from the C_7 stereocenter production. A similar approach was recently reported by Walba and co-workers in a model system directed toward monensin synthesis.[3] In this paper we apply the scheme to yield an efficient, relay synthesis of monensin in which the well-known chromic acid degradation products 2[4] and 3 serve as starting materials.



To separate the bond-forming and chirality-producing steps, we developed a reconstruction via an acetylenic ketone as summarized above. The alkyne/activated ester coupling of A and B thus leads to an ynone having the correct carbon framework and oxidation state of the penultimate precursor, which could then be reduced stereoselectively to the required axial alcohol.

(1) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *Ibid.* **1979**, *101*, 260. Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 262. Collum, D. B.; McDonald, J. H.; Still, W. C. *Ibid.* **1980**, *102*, 2117. Collum, D. B.; McDonald, J. H.; Still, W. C. *Ibid.* **1980**, *102*, 2118. Collum, D. B.; McDonald, J. H.; Still, W. C. *Ibid.* **1980**, *102*, 2120.

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(3) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046.

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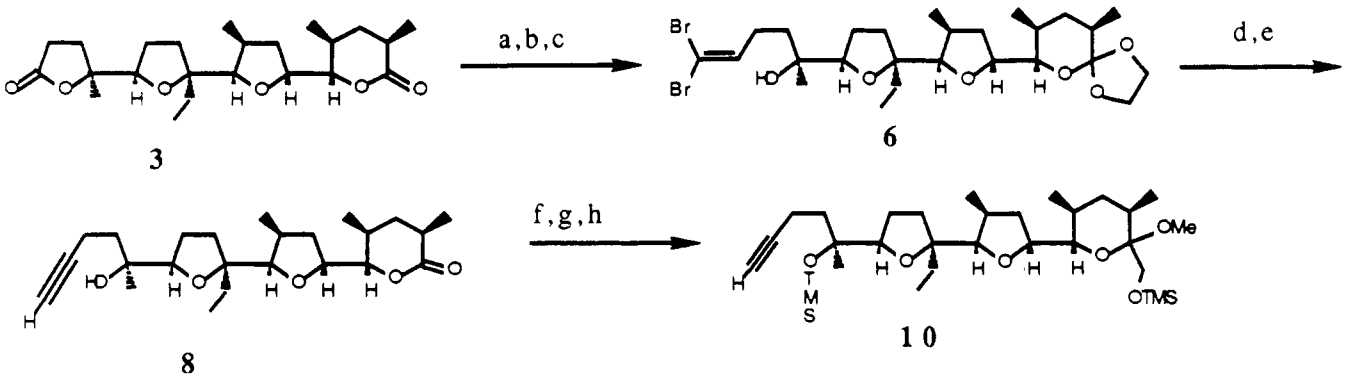
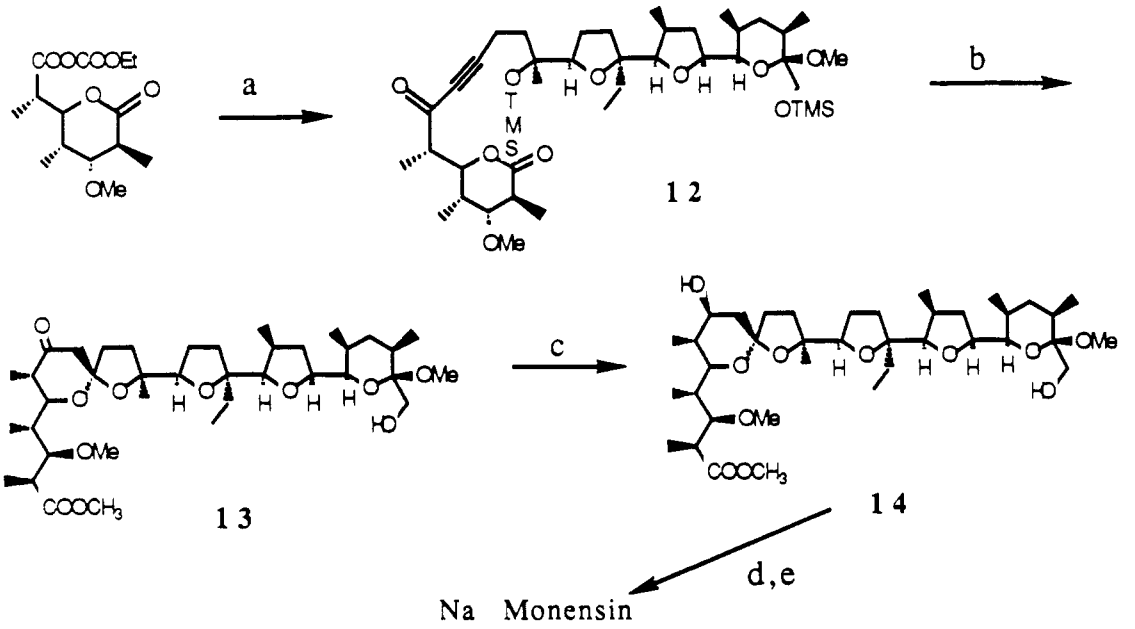
Scheme I[a]



[a] (a) $(HOCH_2)_2$, $HC(OMe)_3$, TsOH, 77%; (b) Dibal, 93%; (c) $Ph_3P{=}CBr_2$, 87%; (d) *n*-BuLi, 96%; (e) TsOH, CH_2Cl_2, H_2O, 100%; (f) $LiCH_2OCH(CH_3)OCH_2CH_3$, −78 °C, 67%; (g) TsOH, CH_3OH, CH_2Cl_2, $HC(OMe)_3$, 93%; (h) TMS–imidazole, 96%.

Scheme II[a]



[a] (a) **10**, *n*-BuLi, $MgBr_2$, THF, 87%; (b) CH_3OH, $NaHSO_4$, 85%; (c) K-Selectride, THF, 91%; (d) NaOH, CH_3OH, 99%; (e) 1. $HClO_4$, $CHCl_3$; 2. NaOH, 81%.

Preparation of the fragment equivalent to B (**10**) began from **3** as summarized in Scheme I. Thus ortho lactone formation proceeded selectively at the 6-membered carbonyl as we have described previously.[1,5] The unreactivity of the butyrolactone moiety likely stems from the relative strain of sp^3 centers in 5-membered rings and follows the relative hydrolysis rates of 5- and 6-membered lactones. With the starting dilactone thus monoprotected (77% yield), the remaining 5-membered lactone was transformed into hydroxyacetylene **8** via **6** by Dibal reduction and use of Corey's[6] dibromomethylenephosphorane (78% overall). Having served its purpose, the ortho lactone was deprotected and the terminal methanol appendage was added as (ethoxyethyl)lithiomethanol (67%).[7] This organometallic addition to lactone **8** was not without difficulties. A major side reaction, enolization of the lactone, could not be completely surpressed in spite of an extensive study of solvent, metal ion, and protecting group dependence. Under the best conditions with THF at −78 °C, approximately 10% enolization accompanied the addition and resulted in epimerization the α-stereocenter of unreacted lactone to a ~1:1 mixture of stereoisomers. Finally, removal of the ethoxyethyl protecting group with acidic methanol and silylation with neat (trimethylsilyl)imidazole provided the desired right-hand fragment **10** in 36% yield over the entire sequence from the monensin degradation product **3**.

Synthesis of the left-hand fragment corresponding to A above was accomplished by direct formation of the isolable, mixed carbonic anhydride with ethyl chloroformate and triethylamine. Sih has previously used a similar lactone for protection of the C_5 hydroxyl in an aldol construction of premonensin.[8]

As shown in Scheme II, **10** was deprotonated with butyllithium, exchanged with $MgBr_2$, and coupled as the magnesium acetylide with **11** to yield the acetylenic ketone **12** in 87% yield. Treatment of the product with acidic methanol then converted **12** into **13** in 85% yield after two

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recycles. During the spirocyclization, a β-alkoxy enone was formed as a major byproduct. This enone appeared to be in equilibrium with spiroketal **13** and could be converted to the original mixture containing more **13** upon isolation and further treatment with acidic methanol.

Studies for the conversion of **13** to monensin were aided by an alternative, more direct prepartion of **13** from methyl monensin. Thus monensin methyl ester could be protected as the C_{25},C_{26} benzylidene derivative (PhCHO, $ZnCl_2$), oxidized to the C_7 ketone (PCC, CH_2Cl_2), and deprotected (H_2, Pd/C, MeOH) to **13** in approximately 40% overall yield.

The last strategic operation was reduction of the C_7 ketone to the axial hydroxyl of monensin. Previous work here had shown that certain 7-keto derivatives of monensin yielded the natural axial 7-hydroxyl configuration with very high stereoselection upon simple reduction with sodium borohydride in methanol, and we attributed at least part of the stereocontrol to the hindrance provided by the 1,3-axial 9-alkoxy group on the cyclohexanoid ring. The situation, however, would appear to be somewhat more complicated since the stereoselectivity of the borohydride reduction was lost upon addition of the terminal methanol side chain of **14**. It is likely that, as found in the X-ray crystal structure of monensin itself, the right-hand half of **14** and related molecules folds back toward the spiroketal ring system and thus places structurally remote features close to the C_7 carbonyl. While various borohydride reagents failed to provide **14** cleanly, borane–dimethyl sulfide complex provided the desired axial alcohol with 8:1 stereoselection (82% yield), and K-Selectride[3,9] (Aldrich) gave it exclusively (91% yield). Practically speaking, however, exceptionally high stereoselection is not critical to the synthesis since the minor epimer resolves from **14** with an R_f difference of more than 0.2 on silica gel.

Final conversion to monensin followed previous work[1] and lead to sodium monensin by saponification, methyl ketal hydrolysis, and salt formation in 81% yield overall. It was necessary to conduct the ketal hydrolysis after saponification of the methyl ester to avoid extensive epimerization at C_{24}. Overall, the construction was a relatively efficient one leading to monensin A from the tetracyclic dilactone **3** in 19% overall yield.[10]

Supplementary Material Available: Complete experimental section (6 pages). Ordering information is given on any current masthead page.

(9) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
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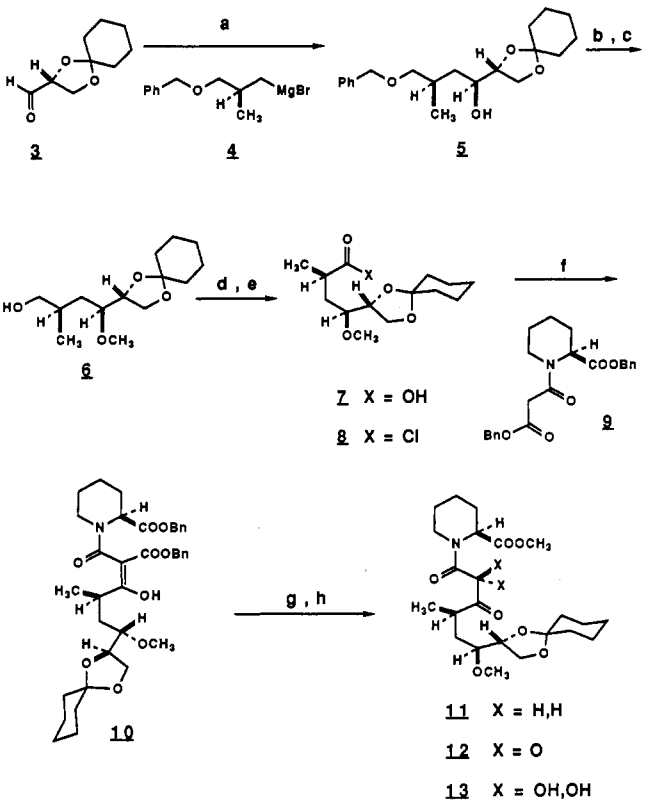
Synthesis of the α,β-Diketo Amide Segment of the Novel Immunosuppressive FK506

Summary: A convenient synthesis of the optically active subunit **2**, incorporating the novel α,β,γ-tricarbonyl system of the potent immunosuppressive macrolide FK506, is described.

Sir: Recently the structure of FK506 was assigned as the novel macrocyclic lactone **1** isolated from *Streptomyces tsukubaensis* (no. 9993).[1] This unique 23-membered macrolide is an important new lead in the search for effective immunosuppressive agents. The exceptional activity of FK506 is reportedly considerably greater, in several assays, than cyclosporin A itself, which is currently the drug of choice in bone marrow and organ transplantations. The natural product contains a peculiar tricarbonyl system as incorporated in the hemiketal, α,β-diketo amide segment ($C_1 \rightarrow C_{15}$). Only two additional antifungal antibiotics, rapamycin[2] and 29-demethoxyrapamycin,[3] have been reported to possess similar functionalization. Rapamycin is currently under investigation by the National Cancer Institute as a potent antitumor agent. Recent efforts of Merck scientists have recorded diastereoselective pathways for preparation of two subunits of FK506 (**1**).[4] We illustrate our studies, providing the first synthetic route to the optically active α,β-diketo amide segment **2** ($C_1 \rightarrow C_{15}$) of the macrolide **1**.

From the onset of our interest, we have assumed that the sequential α,β,γ-tricarbonyl system of **1**, and rapamycin, is essential for biological activity as a site for selective nucleophilic additions. Significant structural fea-

Scheme I[a]



[a] (a) Et_2O, −78 °C, add **4** (75%); (b) dimsyl sodium, DMSO, CH_3I (5 equiv), room temperature (84%); (c) Na (3 equiv), THF liquid NH_3 (90%); (d) THF, Celite, 0 °C, added dropwise 3 M Jones' reagent, 1 h (78%); (e) ClCOCOCl (20 equiv), benzene, +5 → 22 °C, 1 h, (98%); (f) THF, amide **9** (3 equiv), isopropylmagnesium chloride (2 equiv), −10 → 0 °C, 40 min; then **8** in THF (65%); (g) H_2 (1 atm), 10% Pd–C, EtOAc; then CH_2N_2, Et_2O (100%); (h) SeO_2 (1.2 equiv), dioxane, reflux (76%).

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