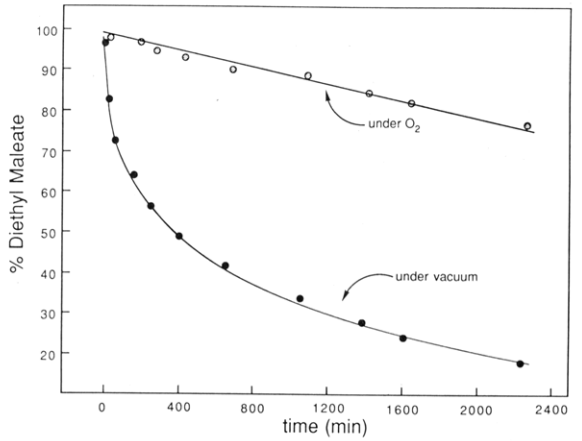
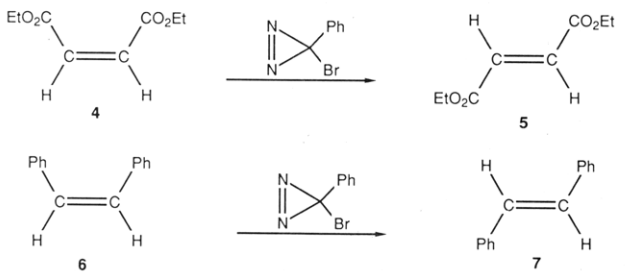


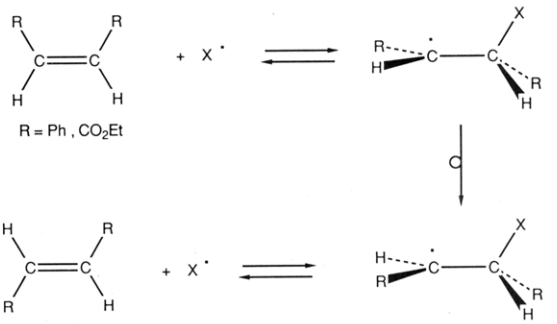
Figure 2. A plot of % unreacted diethyl maleate vs time for isomerization of a 0.44 M solution of diethyl maleate in CCl_4 containing 0.08 M diazirine **1** at 23 °C.

doubt the suggested mechanism for this isomerization which involves formation of the ion pair **3** in a very nonpolar solvent. When the reaction is monitored by NMR in CCl_4 under nitrogen, the disappearance of diethyl maleate is not first order. There is an induction period (which varies from run to run) as shown in Figure 1. In a separate experiment, brief exposure to light from a sunlamp initiates the reaction, which then continues smoothly. Figure 2 shows the result of a third set of experiments. When the reaction is carried out in a degassed solution in a sealed NMR tube under vacuum, there is no induction period. The reaction proceeds at a substantially slower rate under an oxygen atmosphere. In the degassed reaction under vacuum the disappearance of diethyl maleate is still not first order in diethyl maleate. In a fourth set of experiments, addition of thiophenol (PhSH) (which is not consumed during the reaction) also inhibited the reaction relative to the reaction carried out under a nitrogen atmosphere. If the ion pair **3** were involved in the isomerization of diethyl maleate to diethyl fumarate, there should be no induction period or inhibition by oxygen or thiophenol. Furthermore (since the diazirine is not consumed over the course of the reaction) the reaction should be first order in diethyl maleate over the course of the reaction if the ion pair **3** were the catalyzing agent. These experiments are therefore inconsistent with the involvement of the ion pair **3** in the isomerization.



We have found that **1** also catalyzes the isomerization of *cis*-stilbene to *trans*-stilbene.[7] The catalytic behavior is similar to (but not identical with) that observed in the maleate–fumarate isomerization. There is a nonreproducible induction period, and the reaction can be initiated by brief irradiation with a sunlamp. It is important to note that the suggested interaction of the ion pair **3** with the carbonyl group of diethyl maleate cannot occur with *cis*-stilbene. Yet the diazirine **1** catalyzes the isomerization.

These isomerization reactions of diethyl maleate and *cis*-stilbene have characteristics of a free radical chain process. We suggest that a more conventional mechanism initiated by some radical operates in these isomerizations. The nature of the chain-carrying radical is uncertain although bromine atom or phenyldiazirinyl radical initiated processes are likely possibilities. There is therefore no need to suggest the intermediacy of the ion pair **3** in olefin isomerizations.



In summary, our solvolytic studies show that the phenyldiazirinium cation, **3**, cannot be easily generated under solvolytic conditions even in highly ionizing solvents. Furthermore, isomerizations of diethyl maleate to fumarate do not appear to involve this cation. These observations suggest the need for further investigations of processes (such as the reported conductivity measurements) that purportedly involve this cationic intermediate.

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Cobaloxime-Mediated Radical Alkyl–Heteroaromatic Substitution

Summary: The first examples of cobaloxime-mediated radical alkyl–heteroaromatic cross-coupling, replacing a C–H in the protonated heteroaromatic with a C-alkyl, are accomplished via anaerobic visible light photolysis of 95% EtOH solutions of primary and secondary alkyl cobaloximes, $RCo^{III}(dmgH)_2py$ (dmgH = dimethylglyoxime monoanion), and pyridinium, quinolinium, 4-methylpyridinium, benzothiazolium, and benzimidazolium *p*-toluenesulfonate.

Sir: We recently reported radical alkyl–alkenyl cross-couplings via anaerobic visible light photolysis of solutions of $RCo^{III}(dmgH)_2py$ and alkenes activated for attack by nucleophilic alkyl radicals.[2,3] The reactivity of protonated

(1) Fellow of the Alfred P. Sloan Foundation, 1987–1989.

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Table I. Cross-Coupling of 20 mM $RCo^{III}(dmgH)_2py$ with Pyridinium *p*-Toluenesulfonate (2) via Anaerobic Visible Light Photolysis in 95% EtOH Solution

$RCo^{III}Co(dmgH)_2py$	concn of 2 (mM)	products (yield, %)[a,b]
1	200	3 + 4 (47)
1	400	3 + 4 (65)
1	600	3 + 4 (76)
1	800	3 + 4 (87)
1	1000	3 + 4 (87)
5	800	6 + 7 (33–44)
8	800	9 + 10 (68–80)

[a] Yields are combined yields for chromatographically purified mixtures of the 2-substituted and 4-substituted products. [b] Products were obtained in approximately 1:2 ratio of 4-substituted product (3, 6, or 9) to 2-substituted product (4, 7, or 10).

Table II. Cross-Coupling of 20 mM $CH_3(CH_2)_8CH_2Co^{III}(dmgH)_2py$ (1) with Quinolinium *p*-Toluenesulfonate (11) via Anaerobic Visible Light Photolysis in 95% EtOH Solution

concn of 11 (mM)	combined yield (%) of 12 + 13[a]
40	38
200	64
600	80
800	87
1000	86

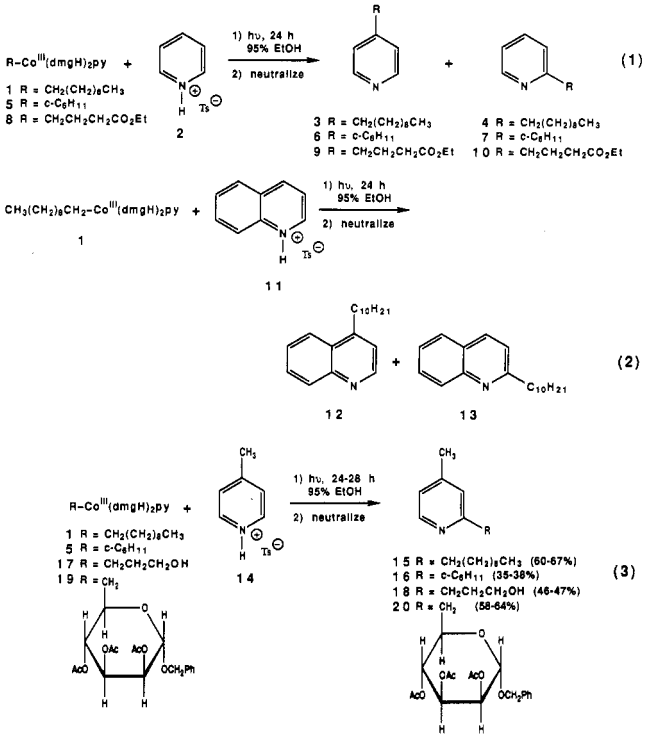
[a] 12 and 13 were obtained in approximately 1:1 ratio.

Table III. Cross-Coupling of 20 mM $RCo^{III}(dmgH)_2py$ with Benzothiazolium *p*-Toluenesulfonate (21) via Anaerobic Visible Light Photolysis in 95% EtOH Solution

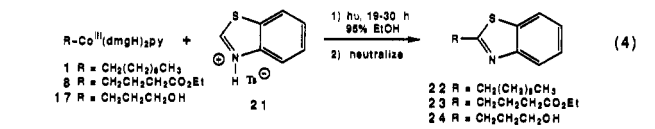
$RCo^{III}(dmgH)_2py$	concn of 21 (mM)	product (yield, %)
1	100	22 (24–28)
1	220	22 (67–69)
1	400	22 (64–66)
1	440	22 (64–70)
1	800	22 (62–64)
8	400	23 (60–63)
17	440	24 (20–21)

heteroaromatics with nucleophilic alkyl radicals is often comparable to the reactivity of activated alkenes.[4] Protonated heteroaromatics thus might be expected to undergo radical cross-coupling with $RCo^{III}(dmgH)_2py$. Based on that premise, we surveyed the feasibility of cobaloxime-mediated radical alkyl–heteroaromatic substitution and report our results here.

We found that anaerobic visible light photolyses[5] of several $RCo^{III}(dmgH)_2py$ with pyridinium *p*-toluenesulfonate (2), quinolinium *p*-toluenesulfonate (11), or 4-methylpyridinium *p*-toluenesulfonate (14) in 95% EtOH led to cross-coupling (eq 1–3; Tables I and II).[6] All reactions were performed by using 20 mM $RCo^{III}(dmgH)_2py$. The concentrations of 2 and 11 are indicated in Tables I and II, respectively. All reactions with 14 used 800 mM 14 (eq 3). The results demonstrate that primary and secondary $RCo^{III}(dmgH)_2py$ can be used and that the reactions are compatible with several common organic functional groups such as hydroxyl, acetate ester carbonyl, benzyl ether C–H, and pyranose acetal C–H.



Protonated benzothiazole is known to be very reactive with nucleophilic alkyl radicals ($k = 1.1 \times 10^6$ M^{-1} s^{-1} for reaction with $^{\bullet}CH_2(CH_2)_3CH{=}CH_2$ at 298 K).[7] The benzothiazole moiety is a carbonyl equivalent and simple, efficient procedures have been developed for its conversion to aldehydes and ketones.[8] The results in eq 4 and Table III demonstrate that cobaloxime-mediated radical alkyl–benzothiazolium cross-coupling is feasible.[6] Our results



(2) (a) Branchaud B. P.; Meier, M. S.; Choi, Y. *Tetrahedron Lett.* **1988**, *29*, 167. (b) Branchaud, B. P.; Meier, M. S. *Tetrahedron Lett.* **1988**, *29*, 3191. (c) Branchaud, B. P.; Meier, M. S. *J. Org. Chem.*, in press. (d) Branchaud, B. P., Choi, Y. L.; Meier, M. S., Yu. G.-X., *J. Org. Chem.*, submitted.

(3) For recent radical–alkene reactions via cobalt radical chemistry, see: (a) Baldwin, J. E.; Li., C.-S. *J. Chem. Soc., Chem. Commun.* **1988**, 261. (b) Coveney, D. J.; Patel, V. F.; Pattenden G. *Tetrahedron Lett.* **1987**, *28*, 5949. (c) Patel, V. F.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1987**, 871. (d) Baldwin, J. E.; Li. C.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166. (e) Scheffold, R. *Pure Appl. Chem.* **1987**, *59*, 363.

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(5) Photolyses were performed by using a 300-W incandescent light bulb in Pyrex test tube reaction vessels in a simple Pyrex apparatus previously described in detail in Branchaud, B. P.; Meier, M. S.; Malekzadeh, M. N. *J. Org. Chem.* **1987**, *52*, 212.

(6) The $RCo^{III}(dmgH)_2py$ 1, 5, 8, 17, and 19 were prepared in moderate to good isolated yields as previously described in ref 2 and 5. Crystalline solid protonated heteroaromatic *p*-toluenesulfonate salts 2, 11, 14, 21, and 25 were prepared from reactions of *p*-toluenesulfonic acid + heteroaromatics and were recrystallized twice from acetone before use. Pyridinium *p*-toluenesulfonate (2) is a known compound and was characterized by ^1H NMR and ^{13}C NMR. Protonated heteroaromatic *p*-toluenesulfonate salts 11, 14, 21, and 25 are new compounds and were characterized by ^1H NMR, ^{13}C NMR, and MS. Products 3, 4, 6, 7, 9, 10, 13, 16, 18, and 24 are known compounds and were characterized by ^1H NMR, ^{13}C NMR, MS, and exact MS (for 13, 18, and 24). Products 12, 15, 20, 22, 23, and 26 are new compounds and were characterized by ^1H NMR, ^{13}C NMR, MS, and exact MS. All yields for cross-coupling products are for isolated, chromatographically purified materials. Yields were determined by ^1H NMR integration vs Ph_3CH added as an internal standard to chromatographically homogeneous samples.

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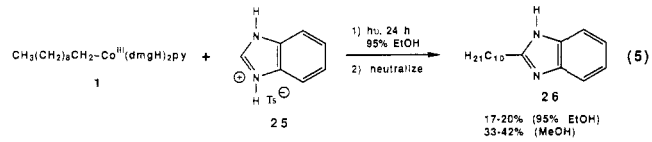
(8) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 5, 9, and 13.

expand the possibilities of using the benzothiazole moiety as a carbonyl equivalent because the radical cross-coupling chemistry is compatible with common organic functionality such as hydroxyl and ester carbonyl that would not be tolerated by the established anionic organolithium and lithium diorganocuprate chemistry.[8]

Several attempts to cross-couple **1** with imidazolium chloride failed to produce any cross-coupling product although **1** was consumed. In contrast, it was possible to cross-couple **1** with benzimidazolium *p*-toluenesulfonate (**25**) (eq 5). Perhaps the positive charge in protonated



(5)

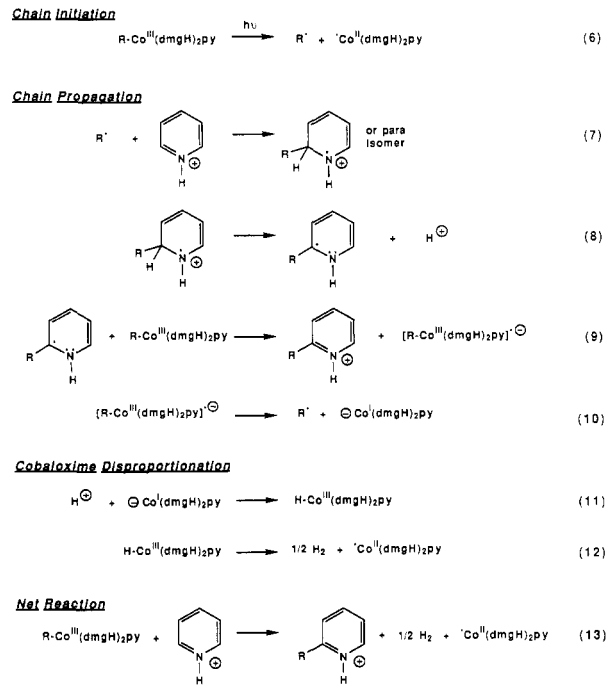
imidazole (pK_a = 6.92)[9] does not provide a sufficient activation for attack by nucleophilic radicals[7b] compared to protonated benzimidazole (pK_a = 5.48),[9] protonated pyridine (pK_a = 5.19),[9] protonated 4-methylpyridine (pK_a = 6.03),[10a] protonated quinoline (pK_a = 4.87),[10b] or protonated benzothiazole (pK_a = 1.2).[10c]

We examined the yield vs concentration of protonated heteroaromatic for cross-coupling of 20 mM **1** with various concentrations of **2** (Table I), **11** (Table II), or **21** (Table III). In all three cases the yields were linear with protonated heteroaromatic concentration at low to moderate concentrations and reached a maximum plateau at higher concentrations. Notably, it takes fewer equivalents of **21** to reach the maximum yield, probably because **21** is more reactive with alkyl radicals than **2** ($k = 4.4 \times 10^4$ M^{-1} s^{-1} for reaction with $^{\bullet}CH_2(CH_2)_2CH_3$ at 330 K)[11] or **11** ($k = 8.5 \times 10^5$ M^{-1} s^{-1} for reaction with $^{\bullet}CH_2(CH_2)_2CH_3$ at 330 K).[11]

Our results can be rationalized by using the mechanistic model of Scheme I, which is directly analogous to the mechanism we previously proposed for cobaloxime-mediated radical alkyl–alkenyl cross-couplings.[2] A somewhat unique feature of our general mechanistic proposal is nonchain radical regeneration and trapping.

Several radical chain alkyl and aryl cross-couplings with protonated heteroaromatics[4] and unprotonated heteroaromatics[12] are known. Of these, the photostimulated radical chain alkylation of pyridine by alkylmercurials[12] is most analogous to our reaction. With use of the pyridine–alkylmercurial system as a model, a radical chain mechanism can be written to account for our results (eq 6–13). Although our data are insufficient to rigorously distinguish between the nonchain (Scheme I) and chain (eq 6–13) mechanisms, we strongly favor the nonchain mechanism based on the following fundamental considerations.

The first branch point in the nonchain vs chain mechanisms occurs in the competition between H-atom abstraction by $^{\bullet}Co^{II}(dmgH)_2py$ from the initial radical-protonated heteroaromatic adduct (Scheme I) vs deprotonation of the initial radical-protonated heteroaromatic adduct (eq 8). We cannot quantitatively analyze this partitioning, but that is irrelevant since we can go one step



further in each mechanism via deprotonation of the initial radial-protonated heteroaromatic adduct (eq 8 and Scheme I) to a second, final branch point which can be quantitatively analyzed. Here the competition is between the electron transfer from a pyridinyl (or other heteroaromatic) radical to $^{\bullet}Co^{II}(dmgH)_2py$ to complete the nonchain mechanism (Scheme I) vs electron transfer from the same pyridinyl (or other heteroaromatic) radical to $RCo^{III}(dmgH)_2py$ to propagate a chain mechanism (eq 9). Consider the differencs in one-electron reduction potentials of $^{\bullet}Co^{II}(dmgH)_2py$ vs $RCo^{III}(dmgH)_2py$ and how that should affect the partitioning of the reaction flux at the electron-transfer branch point. As reasonable models for $^{\bullet}Co^{II}(dmgH)_2py$ and $RCo^{III}(dmgH)_2py$, $CH_3(CH_2)_2CH_2Co^{III}(dmgH)_2BzIm$ (BzIm = benzimidazole) has $E_{1/2}$ = −1.9 to −2.2 V vs SCE[13] whereas $^{\bullet}Co^{II}(dmgH)_2BzIm$ has $E_{1/2}$ = −1.12 V vs SCE.[13] The difference in reduction potential of 0.8 to 1.1 V can be converted via $\Delta G = -nFE$ into an estimated difference of approximately 18.5 to 25.4 kcal/mol in the activation energies of the two competing electron-transfer steps.[14] This predicts that the chain-carrying electron transfer from a pyridinyl (or other heteroaromatic) radical to $RCo^{III}Co(dmgH)_2py$ (eq 9) should be approximately 2.7×10^{14} to 2.3×10^{19} slower than the electron transfer from a pyridinyl (or other heteroaromatic) radical to $^{\bullet}Co^{II}(dmgH)_2py$ to complete a nonchain mechanism (Scheme I). The difference in relative rates is so great that differences in the concentration of $RCo^{III}(dmgH)_2py$ vs $^{\bullet}Co^{II}(dmgH)_2py$ could not significantly alter the basic conclusion of this analysis. In essence, $^{\bullet}Co^{II}(dmgH)_2py$ should act as a chain-terminating radical sca-

(9) *The Merck Index*; Windholz, M., Budavari, S., Blumetti, R. F., Otterbein, E. S., Eds.; Merck & Co., Inc.: Rahway, NJ, 1983; 10th ed.

(10) (a) Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 2, p 171. (b) Reference 10a, p 172. (c) Metzger, J. V., in ref 10a, p 252.

(11) Citterio, A.; Minisci, F.; Franchi, V. *J. Org. Chem.* **1980**, *45*, 4752.

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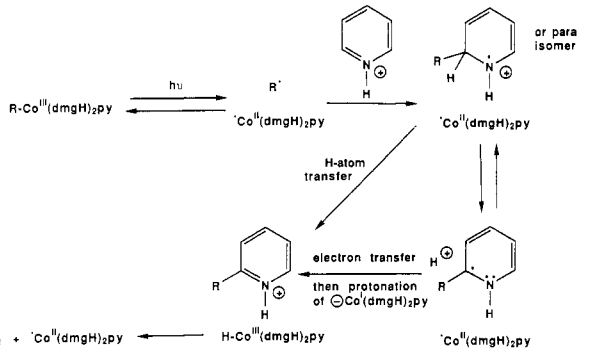
(14) This crude treatment completely ignores the reorganization energy term which is so important in the Marcus theoretical and related empirical treatments of electron transfer. It is likely that the reorganization energy will be similar for the electron-transfer steps which we are comparing, and thus reorganization energy effects would largely cancel out even if a more rigorous analysis of this problem were done. It should be noted that even if the reorganization energies were identical for the two reactions their effects would not completely cancel out because the Marcus-type treatment of electron-transfer reactions provides a quadratic free energy correlation rather than a linear free energy correlation. For a discussion of theories of electron-transfer reactions, see: Eberson, L. *Electron Transfer Reactions in Organic Chemistry*; Springer-Verlag: New York, 1987.

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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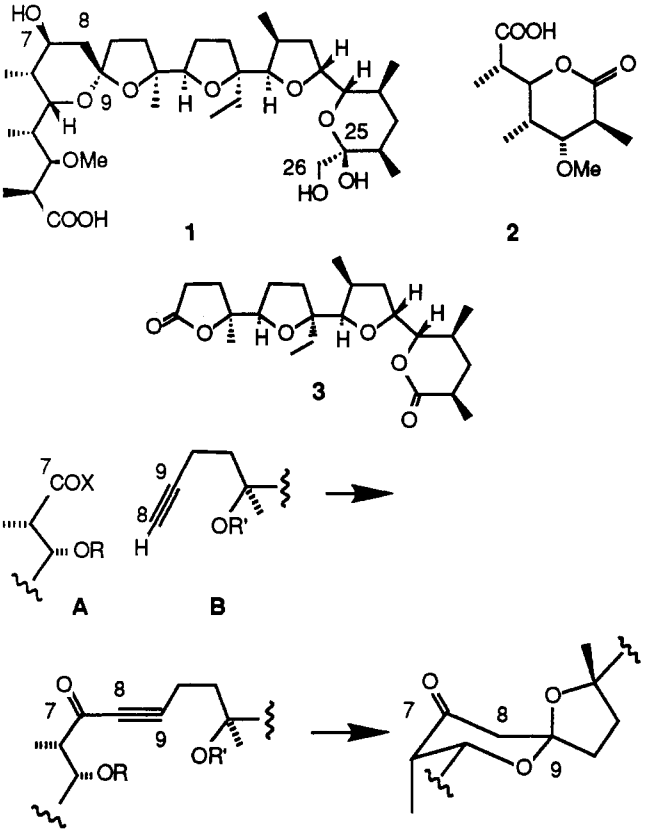
Synthesis of Monensin. Reconstruction from Degradation Products

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.

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