nomenon is only steric or whether an electronic effect is also involved.

After aromatization (DDQ, 50 °C, benzene, 95%) to **10**,[11] cleavage of the phenolic carbonate group (NaOH, C_2H_5OH, 80%) affords the phenol **11**.[6] This substance was expected to give the benzylic acetate **12** upon treatment with $Pb(OAc)_4$ according to the precedent of Garland et al.,[12] but the reaction proved highly complex, and no more than 10% of **12** was isolated under various conditions. Some improvement was obtained with CrO_3–CH_3CO_2H + KF (max 30% of **12**), but other oxidants (PCC, PDC, $Cu(OAc)_2$, $Hg(OAc)_2$, DDQ, Br_2) gave complex products. Methanolic $NaIO_4$ produced the methyl ether **13** (approximately 25%) together with complex byproducts. Finally, it was found that treatment of methyl ether **14** (from **11** + dimethyl sulfate/K_2CO_3) with Br_2 (3 equiv) + CsF in CH_2Cl_2 at −78 °C (2.5 h; quench with cyclohexene) affords the benzylic bromide **15**[6] (65%), together with ring bromination byproducts. In the absence of CsF, complex ring bromination occurs.

The role of fluoride ion can be understood if the attack of Br^+ on the highly substituted aromatic ring is at least partially reversible. Formal bonding of Br^+ at one of the ring carbons in **14** marked by an asterisk places the positive charge adjacent to the Me_3SiCH_2 substituent. Fluoride-initiated desilylation could then give as many as three regioisomeric, nonaromatic trienyl bromides which would rearrange rapidly to the aromatic isomer **15**. This scheme involving fluoride ion interception of some of the intermediates in electrophilic bromination is consistent with results from model studies.[13]

Treatment of **15** with $(C_2H_5)_4N^+CN^-$ produces the desired nitrile **16**[6] (94%), the key substrate for Hassall cyclization, and conversion into **18** via the highly delocalized red anion **17** occurs in 83% yield in the presence of KO-*t*-Bu (3 equiv) in DMF (100 °C). Success requires extreme precautions to exclude oxygen as pointed out by Hassall et al.[1] Anthrone **18**[17] can then be oxidized to the anthraquinone **19**[18] using H_2O_2/NaOH (66%, not optimized). Deprotection of anthraquinone **19** under conditions developed by Kende et al.[19] for the analogous ethylene ketal affords **20**, an intermediate in the synthesis of 11-deoxycarminomycinone.[19,20] These conversions show that Hassall cyclization has promise for synthesis of anthracyclines having base-resistant ring-A substituents.

Efforts are under way to develop similar strategy for anthracycline synthesis where the troublesome C_7 hydroxyl is introduced at an early stage.

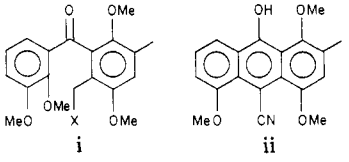
Acknowledgment. This work was supported by PHS Grant CA22937.

Registry No. **1**, 86943-37-5; **2**, 86943-38-6; **3**, 86943-39-7; **4a**, 86943-40-0; **4b**, 86943-41-1; **4c**, 86943-42-2; **4d**, 86943-43-3; **5**, 86943-44-4; **6**, 78725-35-6; *m*-**6**·**4b** analogue, 86943-57-9; *p*-**6**·**4b** analogue, 86943-58-0; *m*-**6**·**4c** analogue, 86943-59-1; *p*-**6**·**4c** analogue, 86943-60-4; *m*-**6**·**4d** analogue, 86953-27-7; *p*-**6**·**4d** analogue, 86943-61-5; *m*-**6**·**9** analogue, 86943-62-6; *p*-**6**·**9** analogue, 86943-63-7; **7**, 86943-45-5; **8**, 86943-46-6; **9**, 86943-47-7; **10**, 86943-48-8; **11**, 86943-49-9; **12**, 86943-50-2; **13**, 86943-51-3; **14**, 86943-52-4; **15**, 86943-53-5; **16**, 86953-26-6; **17**·K^+, 86943-54-6; **18**, 86943-55-7; **19**, 86943-56-8; **20**, 77219-83-1; i (X = $SiMe_3$), 86943-65-9; i (X = Br), 86943-66-0; i (X = CN), 86943-67-1; ii, 86943-68-2; CH_2=CHC(OTBS)=CH_2, 80738-05-2; 3-(trimethylsilyl)propionaldehyde, 18146-03-7; lithioacetylide, 1111-64-4; 5-(trimethylsilyl)-1-pentyn-3-ol, 86943-64-8; 2,3-dimethoxybenzaldehyde, 86-51-1; islandicin trimethyl ether, 50457-06-2.

(11) **10**: 270-MHz NMR (partial, $CDCl_3$) δ 6.98 (s, B-ring aromatic H), 2.40 (br s, Me_3SiCH_2Ar).[6]

(12) Garland, R. B.; Palmer, J. R.; Schultz, J. A.; Sollman, P. B.; Pappo, R. *Tetrahedron Lett.* **1978**, 3669.

(13) Treatment of i (X = $SiMe_3$)[14] with 2.3 equiv of Br_2 + 2.3 equiv of CsF (premixed 1 h at −78 °C) at −78 °C followed by warming to −25 °C and quenching the excess Br_2 with cyclohexene affords i (X = Br) in 89% yield together with a ring-brominated product (7%). When the same experiment is done without CsF, the products include i (X = $SiMe_3$, 18%; X = Br, 52%) and a mixture of ring-brominated and dibrominated byproducts (approximately 20%). The structure of i (X = Br) is proved by conversion to i (X = CN), Hassall cyclization to ii[15] (96%) and oxidation (H_2O_2) to islandicin trimethyl ether[16] (100%).



(14) Miller, W. H. PhD. Dissertation, University of Wisconsin, 1982.

(15) In contrast to **18**, the Hassall product exists as the anthrol tautomer; mp 165–6 °C; 270-MHz NMR ($CDCl_3$) δ 9.4 (s, OH), 7.96 (d, *J* = 7.7 Hz, 1 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 6.96 (d, *J* = 7.7 Hz, 1 H), 6.66 (s, 1 H), CH_3O at 4.08, 4.05, 3.92, CH_3C at 2.45.

(16) We thank Professor C. R. Hutchinson for a comparison sample.

(17) **18**:[6] mp 174–9 °C (ethyl acetate–hexane); 200-MHz NMR (partial, $CDCl_3$) δ 7.92 (dd, *J* = 8, 1 Hz, 1 H), 7.87 (s, 1 H), 7.54 (t, *J* = 8 Hz, 1 H), 7.22 (dd, *J* = 8, 1 Hz, 1 H), 5.47 (s, CHCN), 4.04 and 4.05 (CH_3O singlets).

(18) **19**:[6] mp 165.5–167 °C.

(19) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799. We are grateful to Professor Kende for a generous sample of **20**.

(20) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett* **1980**, *21*, 3351. Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, *48*, 1328.

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Application of Spin-Echo Techniques to the Determination of ^{13}C Labeling Using Proton NMR Spectroscopy

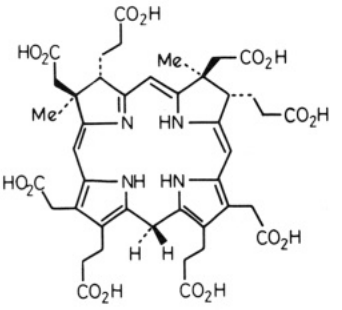
Summary: A simple heteronuclear spin-echo sequence is used for NMR study of a product derived from biosynthetic experiments on vitamin B_{12}. The technique allows observation in the ^1H NMR spectrum of signals only from those protons bonded to ^{13}C. By comparing the results with those previously obtained by using ^{13}C NMR, it is shown that the new technique is quantitatively accurate and considerably more sensitive.

Sir: Recent experiments on the biosynthesis of vitamin B_{12} used a technique of partial ^{13}C labeling of intermediates, the source of the label being [*methyl*-^{13}C]-*S*-adenosylmethionine.[1] Briefly, this work involved enzymic production from the earlier precursor, dihydrosirohydrochlorin[2] (**1**), of cobyrinic acid (**2**) having five of its *C*-methyl groups partially ^{13}C labeled. These methyl groups were those at positions 1, 5, 15, 12α, and 17. It was critical for the successful outcome of the experiments to determine accurately *with a very small sample* the relative amounts of ^{13}C isotope carried by these five *C*-methyl groups. Initially this was achieved by extensive ^{13}C NMR spectroscopy on the heptamethyl ester (**3**) of the labeled cobyrinic acid with careful standardizations. It was found that the

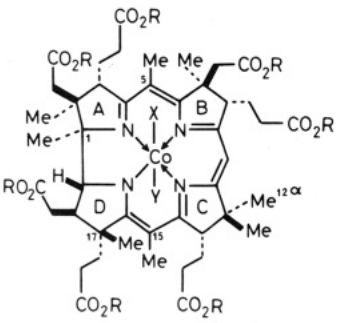
(1) Uzar, H. C.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1982**, 1204.

(2) Battersby, A. R.; Frobel, K.; Hammerschmidt, F.; Jones, C. *J. Chem. Soc., Chem. Commun.* **1982**, 455.

0022-3263/83/1948-3613$01.50/0



(1)



(2) R=H Cobacid
(3) R=Me Cobester

methyl group at C-17 carried considerably less ^{13}C than the other methyl groups. The biosynthetic importance of this result was such (see ref 1) that confirmation was sought by a different approach. Being more sensitive, ^1H NMR spectroscopy would be ideal for this purpose, but a major difficulty is overlap of the much more intense background signals arising from protons *not* coupled to ^{13}C.

A number of techniques[3] have been reported recently for observing in a ^1H NMR spectrum only those protons coupled to ^{13}C; in this communication we describe the first application to a biosynthetic problem of the simplest possible technique that employs the pulse sequences

$$(\pi/2)[H]\text{-}(2J)^{-1}\text{-}\pi[H]\text{-}\pi[C,1,0]\text{-}(2J)^{-1}\text{-acquire } {}^1H,\ \text{receiver add/subtract}$$

In brief, the pulse sequence works as follows. The $(\pi/2)[H]$ pulse, applied along the x axis, rotates the proton magnetization vectors $H_{1/2\alpha}$ and $H_{1/2\beta}$ to the $+y$ axis of the rotating frame. Here, α and β refer to the $\pm z$ eigenstate probabilities of the J-coupled ^{13}C spins. Following a time lapse of $(2J)^{-1}$ s, $H_{1/2\alpha}$ and $H_{1/2\beta}$ have precessed apart π radians and at this stage are aligned one along the $+x$ and the other along the $-x$ axes. Application of a $\pi[C]$ pulse causes the sign of the precessional direction to change, and after a further time period $(2J)^{-1}$, an echo is formed along the $+y$ axis. If $\pi[C]$ is not applied, the echo is formed along the $-y$ axis. Thus, with the receiver working on an add/subtract cycle, a ^{13}C proton doublet will add overall while the background signals cancel. The $\pi[H]$ pulse eliminates precession due to any drift of the chemical shift.

The lower spectrum in Figure 1 shows the upfield region of a normal ^1H NMR spectrum from the partially labeled ^{13}C-cobester[1] (**3**), the minute arrowed signal being one of the ^{13}C satellites from the C-1 methyl. The middle spectrum is the edited version using the foregoing pulse sequence, and comparison of the arrowed signals shows the vast improvement; each labeled methyl group gives a ^1H doublet due to ^{13}C coupling, hence the five doublets. Attention is drawn to the excellent suppression of unwanted resonances. The downfield doublet is the natural abundance satellite from the solvent, benzene. Finally, the top spectrum is the edited version of the ^1H spectrum of cobester (**3**), which had been prepared[1] with *equal* ^{13}C labeling at all C-methyl groups (except the 12β-methyl); this edited spectrum, now with seven doublets, acted as the control for calculation of relative ^{13}C content from the sample of interest (middle spectrum). Integration of the top and middle edited spectra gave results in close agreement with those obtained[1] by direct ^{13}C NMR. In particular, the ^{13}C content of the 17-methyl group was found to be 63% of the standard (cf. 70% by ^{13}C NMR[1]);

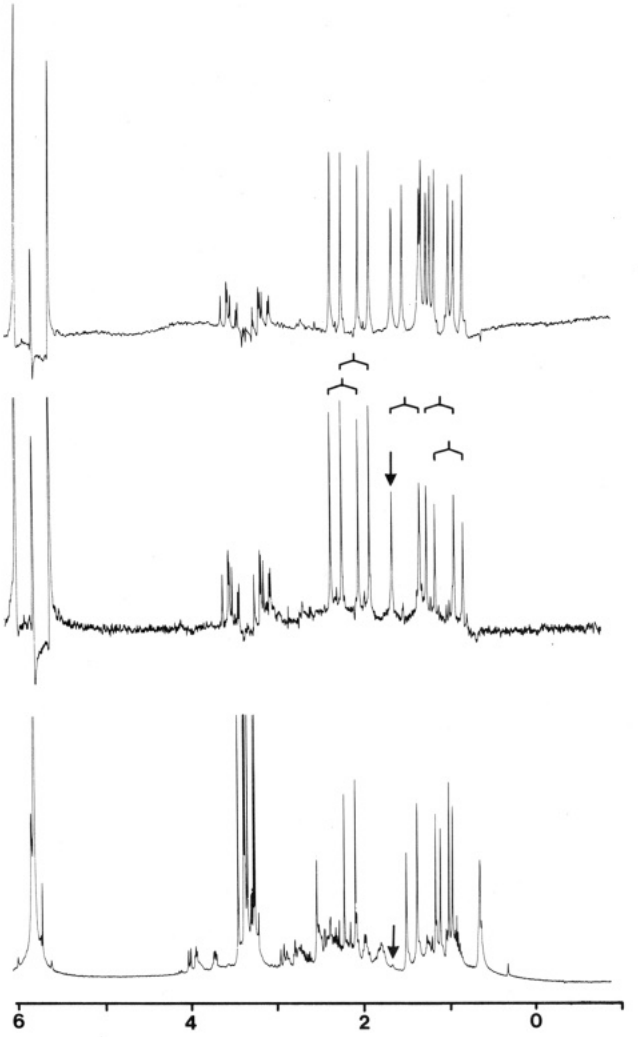


Figure 1. Lower spectrum: normal 400-MHz ^1H NMR spectrum of cobester (**3**) partially labeled with [*methyl*-^{13}C]-*S*-adenosylmethionine.[1] (1.7 mg of sample in 0.3 mL of benzene-d_6; 128 scans were averaged, with a recycle time of 3 s; spectral width 3000 Hz; $t_{90}(^1H) = 21$ μs). Middle spectrum: Edited ^1H NMR spectrum of the above sample using the pulse sequence described in the text (6400 scans were averaged, with a recycle time of 5.72 s; $t_{90}(^{13}C) = 17$ μs). The five ^{13}C-labeled *C*-methyl groups at positions 1, 5, 12α, 15, and 17 of the cobester (**3**) give rise to five ^1H doublets over the region δ 1.0–2.25; average $J = 127.8$ Hz. Upper spectrum: Edited ^{13}C NMR spectrum of the uniformly labeled sample of **3**; see text. The observation conditions were as described above, using 1.67 mg of sample. The seven ^{13}C-labeled *C*-methyl groups at positions 1, 2, 5, 7, 12α, 15, and 17 of **3** give rise to seven ^1H doublets over the region δ 1.0–2.25; average $J = 127.8$ Hz.

(3) Vidusek, D. A.; Roberts, M. F.; Bodenhausen, G. *J. Am. Chem. Soc.* **1982**, *104*, 5452. Freeman, R.; Mareci, T. H.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 341. Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Field, J. *J. Am. Chem. Soc.* **1981**, *103*, 934.

the error range was ±6% in each case. An important difference, however, was that ^{13}C NMR spectroscopy required a longer period of signal averaging to give a spectrum of lower signal/noise ratio than was needed to produce the edited ^{1}H spectrum. The potential is clear for using ^{1}H NMR more generally to follow ^{13}C (or ^{15}N) in biosynthetic research. Not only does this technique offer greater sensitivity (by about an order of magnitude) but the accuracy of cancellation of the unwanted resonances is such that quantitative determinations can be made.

Still further increases in sensitivity (or savings of time) are, in principle, obtainable. A reduction by a factor of 4 in the time required to obtain a given signal/noise ratio could be achieved if the pulse sequence used here were supplemented with ^{13}C broadband decoupling during ^{1}H data acquisition; the spectrum would also appear as a set of singlets. Pulse programmer control would need to be available for both pulse and decouple steps using the ^{13}C excitation channel; most commercial spectrometers lack this facility, and the filling of this gap will further extend the power of isotopic work with ^{13}C.

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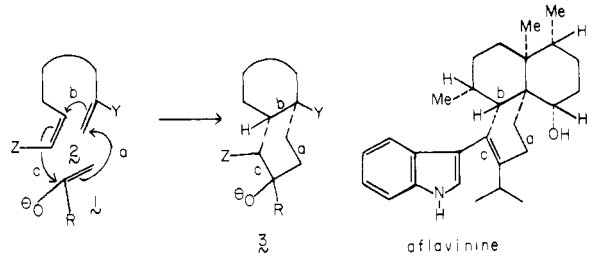
A Stereospecific 2 + 2 + 2 Annulation

Summary: A new strategy for multiple annulation involving sequential Michael and Aldol reactions is described.

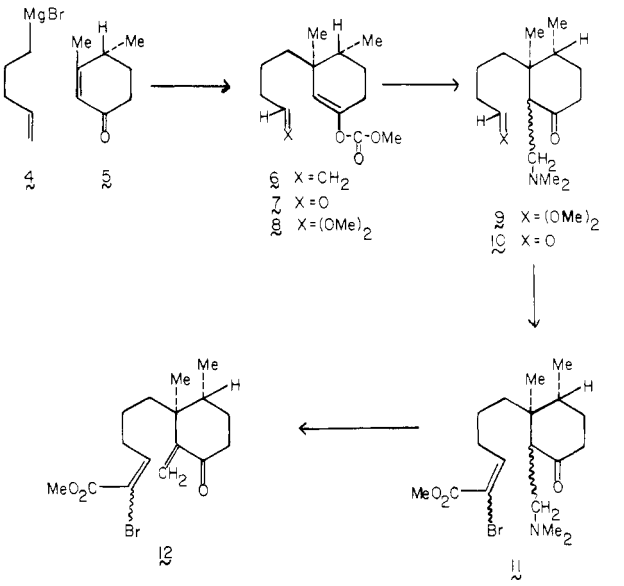
Sir: A tantalizing possibility for assembling polycyclic systems would utilize arrays bearing several centers of electrophilicity. A successful nucleophilic attack generates a new nucleophile that can, in principle, react with another intramolecular electrophile. The synthesis of fused, bridged, and spiro ring systems falls within the scope of this formalism. A proposed synthesis of the novel indolic sesquiterpene aflavinine[1,2] encouraged us to probe the



feasibility of an approach wherein enolate **1** reacts with bis(electrophile) **2**. A sequence of two Michael reactions (see arrows a and b) followed by an aldol reaction (arrow c) is projected to lead to the bicyclic product **3** (see connecting bonds a–c in structure **3** and the corresponding bond possibilities in aflavinine).

The usefulness of the scheme would depend on the efficacy of control elements in the multifaceted ensemble. The initial nucleophile must be directed to the desired electrophilic center. Proton transfers, which might undermine regioconnectivity, are to be avoided. Needless to say, utility will also be closely coupled to the degree of stereoselectivity that pertains. Below we report an experimental realization of such a conjecture.

Reaction of the Grignard reagent **4** with **5** (in 1:1 ether–DMS mediated by CuI) and trapping with methyl chloroformate afforded **6** in 72% yield.[3,4] Compound **6**



was converted to the desired substrate **12** in a six-step sequence in ca. 33% yield. The sequence starts with the previously described selective ozonolysis of the terminal olefin in the presence of the weakly nucleophilic enol carbonate linkage. The aldehyde **7** was converted to its dimethyl acetal **8**.[5] The required lithium enolate, which was exposed by the action of **8** with 3.5 equiv of methyllithium (THF; −78 °C)[6,7], reacts with freshly prepared [(dimethylamino)methylene]ammonium chloride[8] (−78 °C → room temperature) to afford **9**. Crude aldehyde **10**, which was obtained (0.65 N HCl; 15 min, room tempera-

(1) Gallagher, R. G.; McCabe, T.; Hirotsu, K.; Clardy, J.; Nicholson, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 243.
(2) Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. *J. Agric. Food Chem.* **1981**, *29*, 293.
(3) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*,703. Upon scale-up, the yield falls to 72%.
(4) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*, 1419.
(5) Satisfactory NMR, IR, and mass spectra were obtained on all new compounds. Representative data are given below. **8**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H), 1.00–2.40 (m, 11 H), 3.31 (s, 6 H), 3.70 (s, 3 H), 4.32 (t, J = 6 Hz, 1 H), 5.20 (s, 1 H); IR (neat) 1745 cm^{-1}. **11**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 1.00 (d, J = 6 Hz, 3 H), 2.16 (s, 6 H) 1.10–2.60 (m, 14 H), 3.80 (s, 3 H), 6.65 (t, J = 7.5 Hz 0.4 H), 7.26 (t, 7.5 Hz, 0.6 H); IR ($CHCl_3$) 1708, 1720 cm^{-1}. **12**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.03 (s, 3 H), 0.80–2.70 (m, 14 H), 3.80 (s, 3 H), 5.08 (s, 1 H), 5.81 (s, 1 H), 6.61 (t, J = 7.5 Hz, 0.4 H), 7.24 (t, J = 7.5 Hz, 0.6 H); IR ($CHCl_3$) 1690, 1720 cm^{-1}. **15**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.66 (d, J = 7.0 Hz, 3 H), 0.78 (d, J = 7.0 Hz, 3 H), 0.94 (s, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.60–2.40 (m, 16 H), 3.04 (m, 1 H), 3.72 (s, 3 H); IR ($CHCl_3$), 3550, 1715 cm^{-1}. **16** (major diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.61 (s, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 1.00–2.00 (m, 12 H), 2.20 (m, 1 H), 2.40–2.70 (m, 2 H), 3.24–3.40 (m, 2 H), 3.76 (s, 3 H); IR ($CHCl_3$) 1690, 1720, 1740 cm^{-1}. **16** (minor diastereomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.55 (s, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.00–2.25 (m, 14 H), 2.55 (m, 1 H), 2.87–3.00 (m, 1 H), 3.26 (dd, J = 12, 3.5 Hz, 1 H), 3.75 (s, 3 H); IR ($CHCl_3$) 1695, 1725 cm^{-1}. **17**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.64 (s, 3 H), 0.85 (d, J = 6.75 Hz, 3 H), 1.06 (d, J = 6.75 Hz, 3 H), 1.08 (d, J = 6.75 Hz, 3 H), 0.80–2.90 (m, 15 H), 3.50–3.70 (m, 2 H), 9.10 (s, 1 H); IR ($CHCl_3$) 1680, 1640 cm^{-1}.
(6) Cf.: Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.
(7) Holy, N. L.; Wang, U. F. *J. Am. Chem. Soc.* **1977**, *99*, 944.
(8) Kinast, G.; Tietze, L. F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239.

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