Since β-hydroxy amines constitute one of the best recognized classes of pharmacologically active substances, this new method for *predictably* obtaining either desired enantiomer from a racemic mixture should find many practical applications. In addition, β-hydroxy amines are known precursors of epoxides via closure of the derived quaternary ammonium salts.[24] In this way the kinetically resolved amino alcohol in entry 9 was converted in 60% yield to the corresponding epoxide,[25] which was opened with isopropylamine in nearly quantitative yield to give (−)-propranolol.[26] Other chiral epoxides can be similarly prepared.[24,27]

With the emergence of a large new class of substrates the chiral titanium–tartrate complexes have now become asymmetric oxidation catalysts,[28] rather than simply asymmetric epoxidation catalysts.[29] This is the most significant development since the original discovery.[1] Furthermore, we noted earlier,[30] and are still exploring, nonredox asymmetric catalysis by these systems. Thus, we believe that the potential for new applications of these unique nonenzymic titanium catalysts is barely tapped and that before long they will be known simply as asymmetric catalysts.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM28384) and to Eli Lilly for financial support. S.M. thanks the Ministry of Education of Japan for the Overseas Research Fellowship (1982–1983), and S.M.V. thanks the National Science Foundation for a Graduate Fellowship. We thank Dr. Lee Weigel of Eli Lilly for a large sample of (*R*)-(−)-styrene oxide, which greatly eased problems associated with determinations of absolute configuration.

Registry No. (±)-**7**, 87040-32-2; (*R*)-**8**, 87069-57-6; (*S*)-**9**, 87040-33-3; TBHP, 75-91-2; (±)-DIPT, 2217-15-4; $Ti(OiPr)_4$, 546-68-9; (±)-*N*,*N*-dimethyl-β-hydroxyphenethylamine, 2202-68-8; (±)-2-piperidino-1-phenylethanol, 13626-20-5; (±)-*N*,*N*-dibenzyl-β-hydroxyphenethylamine, 87040-34-4; (±)-*N*-benzyl-*N*-methyl-β-hydroxyphenethylamine, 52026-30-9; (±)-1-cyclohexyl-2-pyrrolidinoethanol, 87050-10-0; (±)-1-pyrrolidino-2-decanol, 87040-35-5; (±)-*N*,*N*-dibenzyl-β-hydroxydecylamine, 87040-36-6; (±)-*N*-benzyl-*N*-(3,4-dimethoxyphenethyl)-2-hydroxy-3-(*m*-tolyloxy)propylamine, 87040-37-7; (±)-*N*,*N*-dimethyl-2-hydroxy-3-(1-naphthyloxy)propylamine, 87040-38-8; (±)-*N*-benzyl-*N*-isopropyl-2-hydroxy-3-(1-naphthyloxy)propylamine, 87069-61-2; (±)-*N*-benzyl-*N*-isopropyl-β-hydroxyphenethylamine, 87040-39-9; (±)-*N*-methylephedrine, 1201-56-5; (±)-*N*-methylpseudoephedrine, 87040-40-2; *cis*-(±)-2-(dimethylamino)cyclohexanol, 21651-80-9; *trans*-(±)-2-(dimethylamino)cyclohexanol, 21651-78-5; (±)-*N*,*N*-dimethyl-β-hydroxy-α-phenylethylamine, 2202-64-4; (±)-*N*,*N*-dimethyl-3-hydroxy-3-phenylpropylamine, 36296-95-4; (*R*)-*N*,*N*-dimethyl-β-hydroxyphenethylamine, 34469-09-5; (*R*)-2-piperidino-1-phenylethanol, 40116-77-6; (*R*)-*N*-benzyl-N-methyl-β-hydroxyphenethylamine, 87098-81-5; (*R*)-1-cyclohexyl-2-pyrrolidinoethanol, 87098-82-6; (*R*)-1-pyrrolidino-2-decanol, 87069-58-7; (*S*)-*N*-benzyl-*N*-(3,4-dimethoxyphenethyl)2-hydroxy-3-(*m*-tolyloxy)propylamine, 87069-59-8; (*S*)-*N*,*N*-dimethyl-2-hydroxy-3-(1-naphthyloxy)-propylamine, 87069-60-1; (*S*)-*N*-benzyl-*N*-isopropyl-2-hydroxy-3-(1-naphthyloxy)propylamine, 53729-51-4; (−)-*N*-methylephedrine, 552-79-4; (−)-*N*-methylpseudoephedrine, 14222-20-9; (1*R*,2*S*)-2-(dimethylamino)cyclohexanol, 21651-71-8; (1*R*,2*R*)-2-(dimethylamino)cyclohexanol, 29783-02-6; (*R*)-*N*,*N*-dimethyl-β-hydroxy-α-phenylethylamine, 2202-65-5.

Supplementary Material Available: Determination of absolute configurations and details related to measurement of enantiomeric excesses of β-hydroxy amines (8 pages). Ordering information is given on any current masthead page.

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(24) (a) McClure, D. E.; Engelhardt, E. L.; Mensler, K.; King, S.; Saari, W. S.; Huff, J. R.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 1826. (b) Lyle, G. G.; Keefer, L, K. *Ibid.* **1966**, *31*, 3921. (c) Coke, J. L.; Richon, A. B. *Ibid.* **1976**, *41*, 3516 and references cited therein.

(25) The procedure of McClure et al.[24a] was followed.

(26) This step is identical with the final step in our previous synthesis of (−)-propranolol.[3]

(27) Of the various[24] procedures for closing a β-hydroxy quaternary ammonium salt to an epoxide, we find the NaH/DMF method of McClure et al.[24a] to be the most convenient, since DMF is also a good solvent for the alkylation with methyl iodide.

(28) In the present work, to realize a decent oxidation rate with only 0.6 equiv of TBHP, we use stoichiometric amounts of the titanium–tartrate complex. With more TBHP and/or longer reaction times we have seen more than one turnover per metal center, but under these conditions the enantioselectivity is also poorer. While the achiral oxidation of β-hydroxy amines with TBHP is the presence of $Ti(OR)_4$ is catalytic in the metal species,[7] it remains to be established whether this enantioselective version can be regarded as truly catalytic. The *N*-oxide product appears to be a strong inhibitor of the desired catalysis.

(29) We are now seeking to further generalize these enantioselective oxidations among the family of substrates shown in Scheme II.

(30) See footnote 16 in ref 4, which describes diastereo- and enantioselective openings of racemic epoxy alcohols by the titanium–tartrate catalyst.

Silicon-Mediated Synthesis of 11-Deoxyanthracyclines

Summary: The Hassall cyclization (**17** → **18**) has been used as a key step in the synthesis of 11-deoxycarminomycinone. Other steps include the unusual Diels–Alder addition **6** + **4a** → **7**, where the directing effect of dienol carbonate oxygen is dominated by other substituents. A benzylic silane serves as a latent leaving group and is converted into benzylic bromide (**14** → **15**) by treatment with Br_2/CsF.

Sir: We have developed a route to 11-deoxyanthracyclines based on the Hassall cyclization (as in **17** → **19**) approach to anthraquinones.[1] Key features of the sequence include good control of regiochemistry and the use of benzylic silicon as a latent leaving group.

Diels–Alder condensation of ynone **1**[2] with CH_2=CHC(OTBS)=CH_2 (Scheme I) affords the adduct **2** (75–80%, 185 °C).[5,6] Selective conversion of enol ether **2** to monoketal **3** (80%) occurs with 2,2-dimethylpropanediol (5 equiv) and camphorsulfonic acid (THF, 20 °C). Attachment of the remaining anthracycline carbons involves Diels–Alder condensations of dienyl ether derivatives such as **4**. Under the best enolization conditions found (LDA in THF + TMEDA, −100 °C), an 8:1 ratio of **4a** and the undesired γ-deprotonation product **5** is obtained after quenching with $ClCO_2Et$.[7]

(1) Davies, J. S.; Davies, V. H.; Hassall, C. H. *J. Chem. Soc. C* **1969**, 1873. Hassall, C. H.; Morgan, B. A. *J. Chem. Soc. D* **1970**, 1345; *J. Chem. Soc., Perkin Trans. 1* **1973**, 2853. Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Ibid.* **1977**, 2502.

(2) Prepared from 3-(trimethylsilyl)propionaldehyde[3] and lithioacetylide[4] (−78 °C, 30 min; warmed to 20 °C; distilled ynol product, bp 55–8 °C, 0.8 mm) followed by two-phase Jones oxidation (ether as organic phase, 10 °C) to give **1** (bp 57–8 °C, 3 mm), 70% overall yield.

(3) Picard, J.-P.; Ekouya, A.; Dunogues, J.; Duffaut, N.; Calas, R. *J. Organomet. Chem.* **1975**, *93*, 51.

(4) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

(5) **2**: crystallized from hexane, mp 32–5 °C; 270-MHz NMR ($CDCl_3$) δ 6.78 (br s, 1 H), 4.91 (br t, *J* = 2.5 Hz, 1 H), 2.94 (m, 4 H), 2.63 (m, 2 H), 0.94 (s, 9 H), 0.79 (m, 2 H), 0.16 (s, 6 H), 0.02 (s, 9 H).

(6) Correct composition by high-resolution mass spectroscopy.

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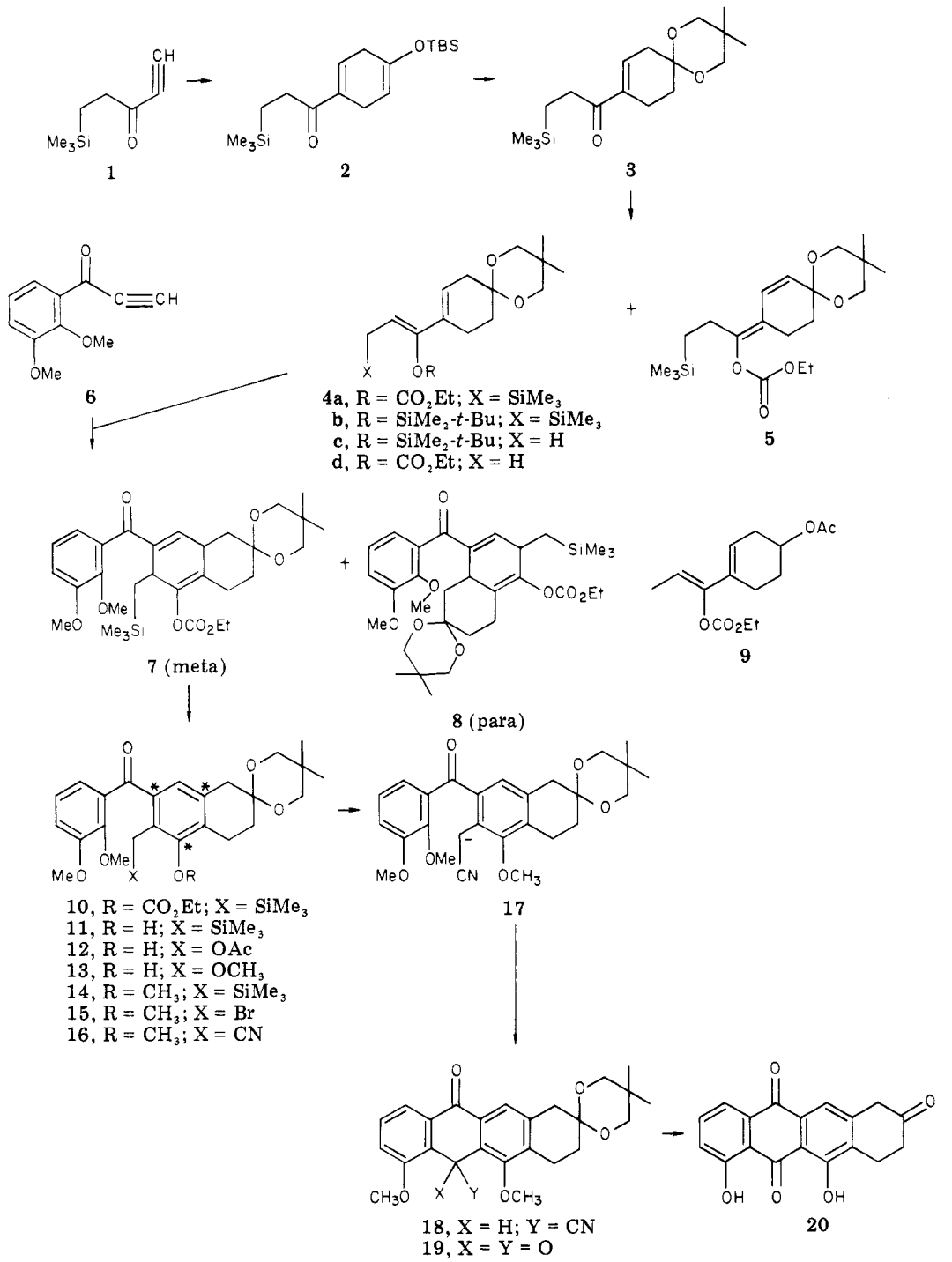
Scheme I



Condensation of **4a** with ynone **6**[8] (toluene, 130 °C) affords 84–87% of meta adduct **7**![9] The para regioisomer **8** is also formed (8%).[9] This remarkable selectivity of 11:1 meta:para results from several additive substituent effects which override the normal para-directive influence of the diene oxygen substituent relative to dienophile carbonyl. These effects have been probed by studying the condensations of **6** with **4b** (meta:para = 4:7), **4c** (meta:para = 2:9), **4d** (meta:para = 7:4), and **9** (meta:para = 2:3). The results indicate that enol carbonate is a weak para-directing group compared with enol silane and that allylic silicon directs in favor of the meta product,[10] as does the ketal substituent. We do not know whether this latter phe-

(7) Without TMEDA, the ratio is 5:1, and HMPA in place of TMEDA affords a ratio of 1:2. The ethylene ketal analogous to **3** gives a 1:1 mixture of α and γ deprotonation products, a result reminiscent of findings by Gesson et al.: Gesson, J. P.; Jacquesy, J. C.; Mondon, M. Tetrahedron Lett. **1980**, *21*, 2509.

(8) Prepared from 2,3-dimethoxybenzaldehyde and lithioacetylide[4] (−78 °C, 20 min; warmed to 20 °C) followed by two-phase Jones oxidation (1:4 ether:CH_2Cl_2 as organic phase, 30 min, 0 °C) 72% overall yield: mp 51–2 °C (ethyl acetate–hexane); NMR ($CDCl_3$) δ CH_3O at 4.0 and 3.95, HC≡C at 3.48 (s).

(9) **7** (R_f 0.23, TLC on silica gel, 10% ethyl acetate–hexane, four elutions); **8** (R_f 0.3). 270-MHz NMR (partial, $CDCl_3$) δ **7**[6] [6.22 (d, J = 4 Hz, enone β-H), methoxyl singlets 3.87, 3.76]; **8**:[6] [6.35 (d, J = 4 Hz, enone β-CH), methoxyl singlets 3.86, 3.78]; regiochemistry assignments confirmed by decoupling studies.

(10) The directive effect of allylic silicon on Diels–Alder regiochemistry has been observed before: Wilson, S. R.; Phillips, L. R.; Natalie, K. J. *J. Am. Chem. Soc.* **1979**, *101*, 3340. Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 355. Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534.

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.

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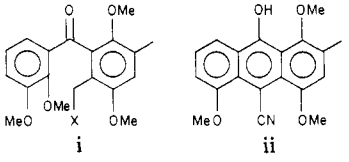
Registry No. **1**, 86943-37-5; **2**, 86943-38-6; **3**, 86943-39-7; **4a**, 86943-40-0; **4b**, 86943-41-1; **4c**, 86943-42-2; **4d**, 86943-43-3; **5**, 86943-44-4; **6**, 78725-35-6; *m*-**6**·**4b** analogue, 86943-57-9; *p*-**6**·**4b** analogue, 86943-58-0; *m*-**6**·**4c** analogue, 86943-59-1; *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.

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