A Convergent, Highly Stereoselective Synthesis of a C-11–C-21 Subunit of the Macbecins

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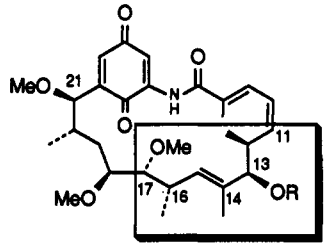
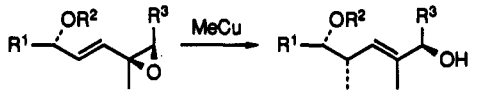
Received June 26, 1991

Summary: Acetonide **20**, a possible synthetic precursor of the macbecins, was prepared by a highly stereoselective route from the enantiomeric methyl 3-hydroxy-2-methylpropionates. A key step involved anti S_N2' addition of $Me_2Cu(CN)Li_2$ to vinyloxirane **15** to effect stereoselective introduction of the allylic CH_3 center and the *E*-trisubstituted double bond.

Macbecin I and related ansamycin natural products exhibit broad-spectrum antibiotic, antiviral, and antitumor activity.[1,2] In connection with a program on the synthesis of such compounds, we initiated studies on the S_N2' addition of organocopper reagents to acyclic vinyloxiranes such as **I**.[3] Our findings indicated that these reactions proceed with good to excellent anti stereochemistry, depending on the nature of the cuprate and the R^2 substituent in **I**.[4,5] The present work was aimed at a total synthesis of the C-11 to C-21 subunit of the macbecins by a route in which the common C-13–C-17 array would be assembled through application of this technology.

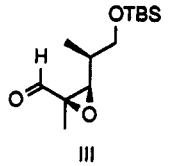


Macbecin I R = $CONH_2$



I **II**

The key vinyloxirane intermediate **15** (or **16**) was prepared through Horner–Emmons coupling of epoxy aldehyde **III**[5] with keto phosphonate **13**. The latter was synthesized according to Scheme I starting from the reduction product **1** of the *t*-$BuPh_2Si$ (TBDPS) derivative of (*R*)-methyl 3-hydroxy-2-methylpropionate. Homologation by cyanide displacement on mesylate **2**, followed by reduction and hydrolysis, afforded the aldehyde **4**, which was directly subjected, without purification, to Wittig condensation then reduction to allylic alcohol **6** in 75% yield based on nitrile **3**. Sharpless epoxidation of allylic alcohol **6** at −30 °C yielded epoxy alcohol **7** as a 95:5 mixture of diastereoisomers.[6]



III

After some trials with several procedures we developed an efficient conversion of epoxy alcohol **7** to the allylic ether **10** by sequential treatment of the derived iodide **8** with *n*-BuLi and $(MeO)_2SO_2$.[7] An alternative two-step procedure involving treatment of the alcohol **9** with NaH, THF–DMF, and then MeI led only to desilylated material.[8]

Ozonolysis of allylic ether **10** followed by reductive workup (Me_2S) afforded aldehyde **11** in only 30% yield. Furthermore, addition of dimethyl (lithiomethyl)-phosphonate to aldehyde **11** then Dess–Martin oxidation led to keto phosphonate **13** in only 12% yield.[9] In view of these unpromising results we explored methodology for the efficient conversion of allylic ether **10** to the ester **12**. Attempts at oxidation of aldehyde **11** to the acid with a variety of reagents were unpromising. In searching for alternative oxidizing agents we came upon a report by Djerassi describing the conversion of steroidal aldehydes to esters, in moderate yield, by the action of ozone in methanolic KOH.[10] Reasoning that the primary ozonide of allylic ether **10** could give rise to aldehyde and/or a hydroperoxy mixed acetal in situ and that each of these intermediates could lead to the ester by an analogous process, we examined the ozonolysis of **10** in KOH–MeOH with CH_2Cl_2 as a convenient cosolvent. As predicted, the ester **12** was thereby produced in a remarkable 98% yield. Judging from the spectral characteristics of subsequent products, no epimerization of ester **12** occurred despite the alkaline reaction conditions. Addition of dimethyl (lithiomethyl)phosphonate to ester **12** afforded the keto phosphonate **13** in 78% yield.

Horner–Emmons condensation of keto phosphonate **13** with epoxy aldehyde **III** proceeded readily to afford the enone **14** in 80% yield. Chelation-controlled reduction of the ketonic grouping with $Zn(BH_4)_2$ gave the desired alcohol **15** with >20:1 diastereoselectivity.[11] Unfortunately, the Lewis acidic Zn salts cause partial decomposition of the sensitive vinyloxirane function. With less acidic reducing agents (DIBAH, $NaBH_4$) the yield of alcohol was >90% but disastereoselectivity was quite low.

Treatment of vinyloxirane **15** with Me_2CuLi or MeCu(CN)Li under conditions previously employed for **I** → **II** (R^2 = H) led only to recovered starting material.[5] Surprisingly, the higher order cuprate, $Me_2Cu(CN)Li_2$,[12] gave the best results with vinyloxirane **15** affording over 60% of an 11:1 mixture of S_N2' product **17** and S_N2 product along with 8% of 1,3-diene product.[13] In the model system

(1) Tanida, S.; Hasegawa, T.; Higashide, E. *J. Antibiot.* **1980**, *33*, 199. Muroi, M.; Izawa, M.; Kasai, Y.; Asai, M. *J. Antibiot.* **1980**, *33*, 205. Muroi, M.; Haibara, K.; Asai, M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123.

(2) For previous synthetic studies see: (a) Baker, R.; Cummings, W. J.; Hayes, J. F.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1237. Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. I* **1989**, 190. Total synthesis of (+): Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378. (b) Coutts, S. J.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301. Formal synthesis of (±): Coutts, S. J.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4305.

(3) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.

(4) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *56*, 2225.

(5) Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1990**, *55*, 1540.

(6) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(7) Alternative methodology involving telluride-induced reduction-elimination of epoxy mesylates has recently been reported. Discordia, R. P.; Murphy, C. K.; Dittmer, D. C. *Tetrahedron Lett.* **1990**, *31*, 5603. We thank Professor Dittmer for a preprint of this paper.

(8) Cf. Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669.

(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(10) Sundararaman, P.; Walker, E. C.; Djerassi, C. *Tetrahedron Lett.* **1978**, 1627.

(11) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

(12) Cf. Lipschutz, B. H. *Synthesis* **1987**, 325.

(13) This product may arise through elimination of the intermediate Cu(III) adduct with concommitant loss of the neighboring OH grouping.

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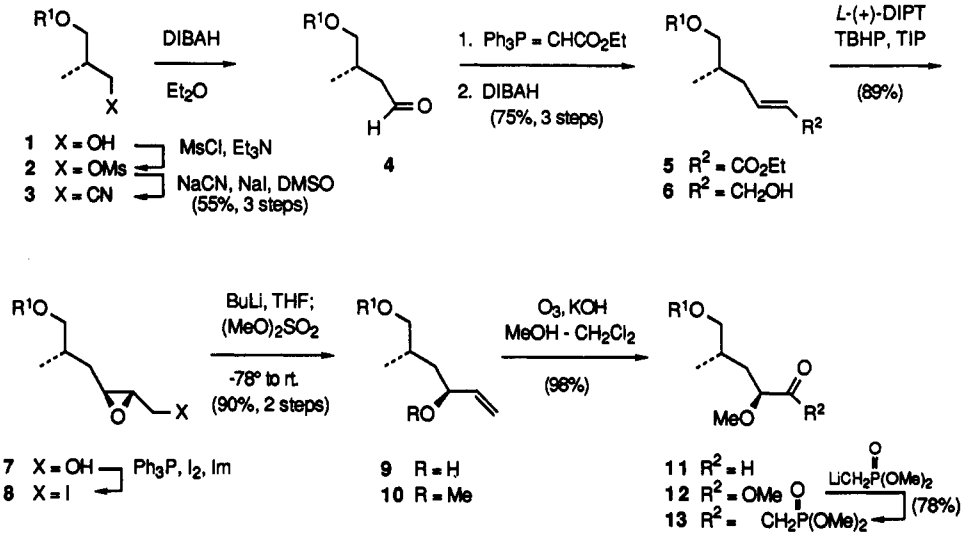
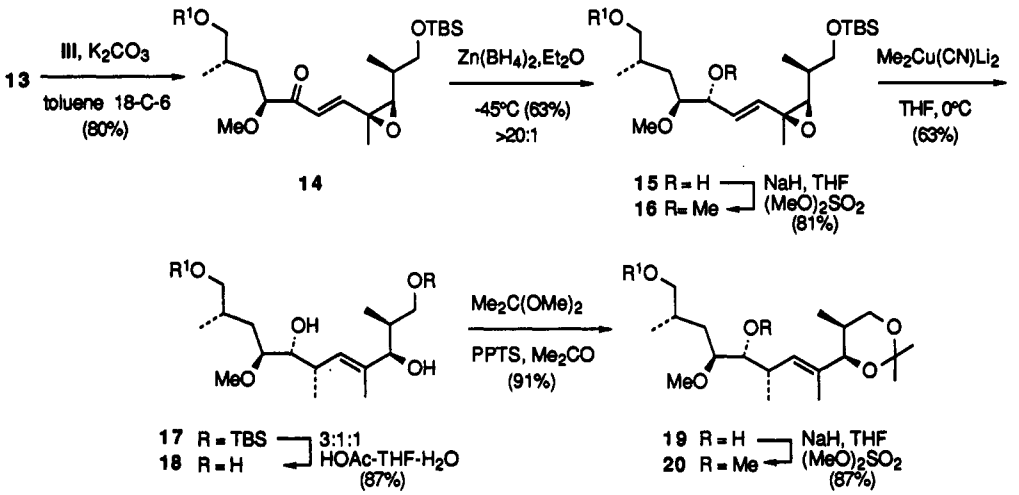
Scheme I[a]



[a] R^1 = *t*-BuPh$_2$Si.

Scheme II[a]

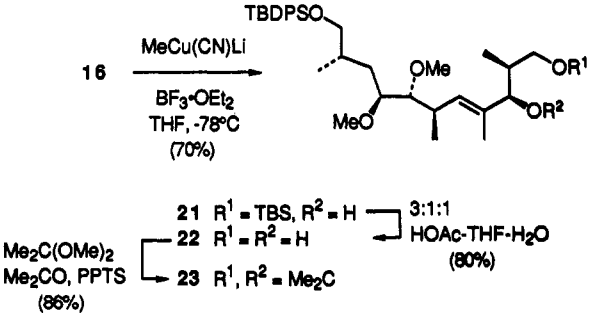


[a] R^1 = *t*-BuPh$_2$Si.

I (R^1 = Me, R^2 = H, R^3 = CH_2OMOM), this cuprate yielded a 62:38 mixture of S_N2':S_N2 products and no 1,3-diene.[4]

Differentiation of the two secondary alcohol groupings of diol **17** was achieved by selective hydrolysis of the primary TBS ether followed by formation of the cyclic acetonide **19**. O-Methylation of **19** led to the macbecin I subunit **20**.

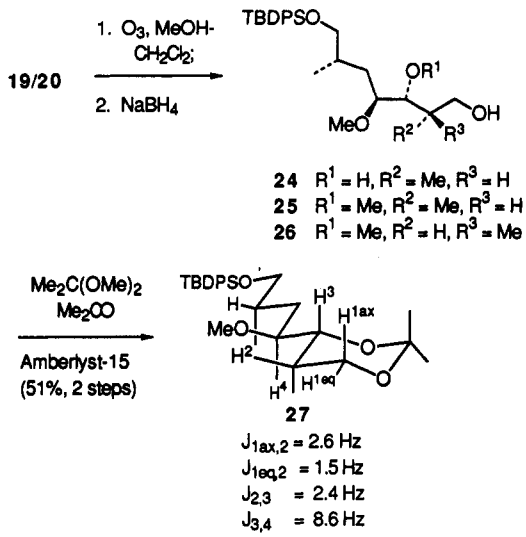
As an alternative route to **20** we examined cuprate additions to the methyl ether **16**. Treatment of **16** with the higher order cuprate $Me_2Cu(CN)Li_2$, as for **15**, gave only the diene resulting from elimination, a result consistent with our earlier studies.[4,13] With Me_2CuLi, a mixture of S_N2', S_N2, and elimination product was obtained. The use of MeCu(CN)Li in the presence of BF_3·OEt_2 proved successful, leading to a 20:1 mixture of S_N2':S_N2 products in 70% yield.[14] The S_N2' product **21** was converted to the cyclic acetonide **23** as described for **17**. Surprisingly, the acetonides (**20** and **23**) prepared by the two routes were found to be isomers by comparison of their spectra. The ^{13}C NMR spectrum of each showed vinyl CH_3 peaks near 15 ppm indicative of an *E* double bond.[15] Accordingly, the two were surmised to be epimeric at the CH_3-substituted allylic stereocenter.



Assignment of this stereocenter in alcohol **19** could be made by ozonolysis–reduction and conversion of the diol **24** to the cyclic acetonide **27**. The ^1H NMR coupling constants confirmed the structure as shown. Ozonolysis of the methyl ether **20** followed by reduction yielded alcohol **25**. As expected, the corresponding alcohol **26** from ether **23** was isomeric with **25**. Thus, cuprate addition to

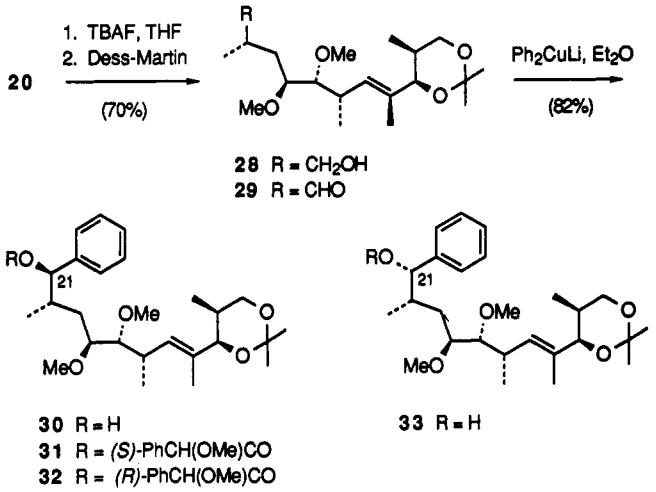
(14) Cf. Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420.

(15) Ravi, B. N.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 2127.



the OH-substituted vinyloxirane **15** proceeds with high anti selectivity, whereas addition to the methyl ether **16** is highly syn selective. Previous studies with TBS and MTM ether prototypes of **16** showed moderate to excellent preferences for anti addition.[4] It is not clear at this point if the methoxy substituent, the use of $BF_3 \cdot OEt_2$, or some conformational factor is responsible for the ususual syn selectivity observed for **16**.

To explore the possibility of using acetonide **20** as a synthetic precursor of the macbecins, we prepared aldehyde **29** by silyl ether cleavage and Dess–Martin oxidation.[9] Addition of Ph_2CuLi to **29** yielded a separable 5.5:1 mixture of diastereomers favoring the Cram–Felkin–Ahn adduct **30**. The stereochemistry of this alcohol, ascertained by ^1H NMR analysis of the *O*-methyl mandelates,[16] is that required for elaboration to the macbecin family of natural products.[17] Therefore, by using an analogous cuprate



derived from the aryl subunit described by Kallmerten[2b] in his recent synthesis, it should be possible to convert aldehyde **29** to macbecin I along the route previously employed by Baker, et al.[2a]

Acknowledgment. This work was supported by a research grant (CHE-8912745) from the National Science Foundation.

(16) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

(17) Satisfactory IR, ^1H NMR, and mass spectra/or combustion analyses have been obtained for all previously unknown synthetic intermediates.

Articles

Medium and Structure Effects on the Anodic Oxidation of Aryl Arylmethyl Sulfides

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Received August 21, 1990

The anodic oxidation of a number of $XC_6H_4CH_2SC_6H_4Y$ has been investigated under a variety of conditions ($AcOH/AcO^-$, $AcOH/NO_3^-$, $AcOH/ClO_4^-$, CH_3CN/ClO_4^-) and the relative weight of the various reaction paths available to the intermediate radical cation (C_α–H deprotonation, C–S bond cleavage, attack on sulfur) evaluated via product analysis. It has been observed that in $AcOH/AcO^-$ (presence of a strong base) the main reaction is C_α–H deprotonation, which is also favored when X is an electron-withdrawing substituent and depressed by electron-donating Y. The C–S bond cleavage reaction is particularly important in CH_3CN/ClO_4^-; its relative contribution is enhanced by an electron-donating X, which makes the benzyl carbocation more stable. The pathway leading to sulfoxides is favored in $AcOH/NO_3^-$ and, to a lesser extent, in $AcOH/ClO_4^-$. Formation of sulfoxide is also favored when Y is an electron-donating group.

In the last few years there has been increasing concern with the role of electron-transfer (ET) processes in organic reactions.[1] Radical ions have been suggested as critical intermediates in a great variety of processes, and moreover,

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(1) Eberson, L. *Electron Transfer Reaction in Organic Chemistry*; Springer-Verlag: Berlin, 1987.

0022-3263/91/1956-5498$02.50/0