Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5657-5660, 1996

0040-4039/96 $15.00 + 0.00

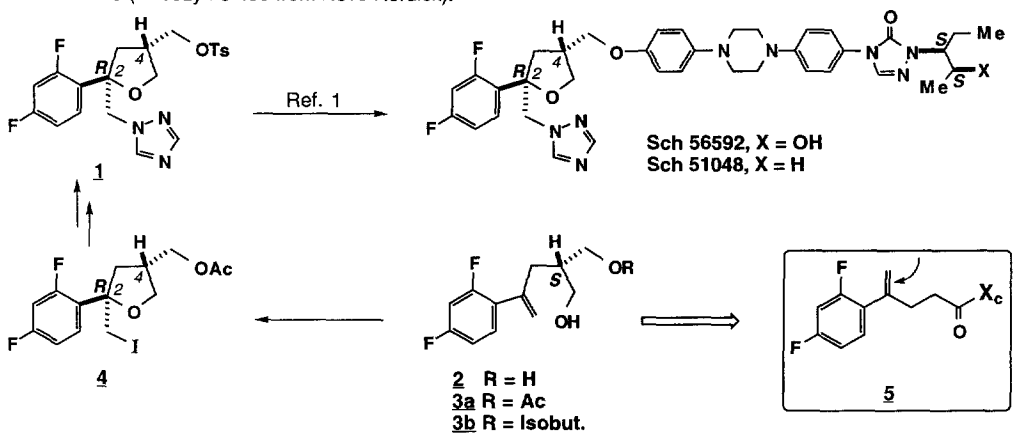
PII: S0040-4039(96)01203-8

CONCISE ASYMMETRIC ROUTES TO 2,2,4-TRISUBSTITUTED TETRAHYDROFURANS VIA CHIRAL TITANIUM IMIDE ENOLATES: KEY INTERMEDIATES TOWARDS SYNTHESIS OF HIGHLY ACTIVE AZOLE ANTIFUNGALS SCH 51048 AND SCH 56592

Anil K. Saksena,* Viyyoor M. Girijavallabhan, Haiyan Wang, Yi-Tsung Liu,* Russell E. Pike and Ashit K. Ganguly.
Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033, U.S.A.

Abstract: Two complimentary approaches to the key (-)-(2R)-*cis*-tosylate **1** and its (+)-(2S)-enantiomer **15** via generation of chiral imide enolates having a 2,2-disubstituted olefin functionality in the β-position, are described. In a "protecting group free" sequence, reaction of the titanium enolate generated from (4R)-benzyl-2-oxazolidinone derived imide **5b** with s-trioxane provided a convenient intermediate **19** which could be directly subjected to 2,4-diastereoselective iodocyclization. Copyright © 1996 Elsevier Science Ltd

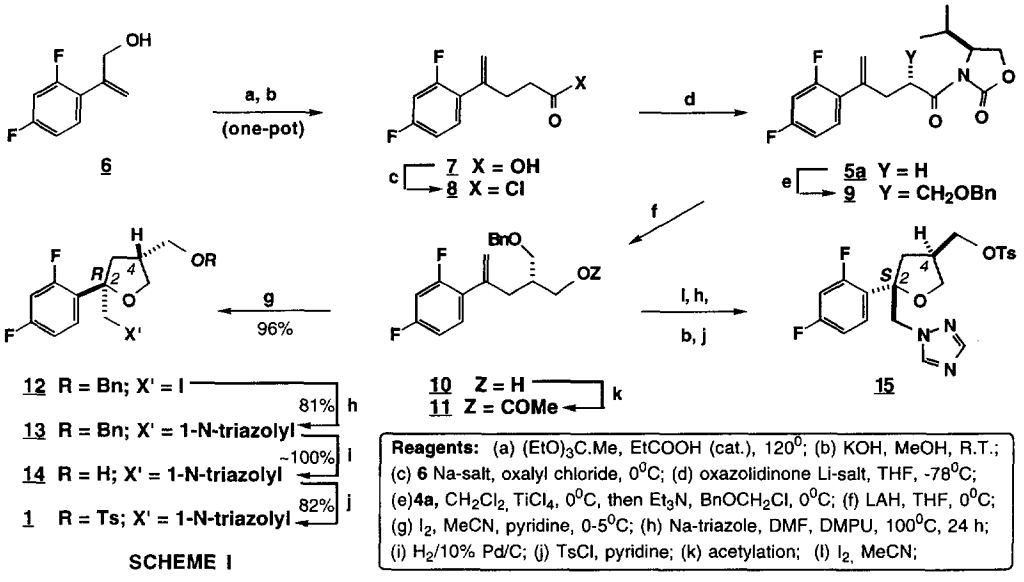
As part of an extensive search for orally effective antifungal agents we recently described a practical synthesis of **Sch 56592** which posesses improved therapeutic potential over **Sch 51048** and other clinically useful agents against a variety of systemic fungal infections in normal and immunocompromised infection models.[1,2] Both compounds belong to an uncommon 2,2,4-trisubstituted *cis*-tetrahydrofuran family of orally active broad-spectrum antifungals. In our earlier chemoenzymatic route to these compounds, the key (-)-(2R)-*cis*-tosylate **1** was secured *via* an unprecedented and remarkably efficient 2,4-diastereoselective 5-exo-halocyclization process. The (4S)-diol monoester synthons **3a** and **3b** of high optical purity (~99% ee) were obtained in this case by organic-phase enzymatic acylation of **2** in the presence of Novo SP 435 (Novozyme 435 from Novo Nordisk).[2]



Enantioselective chemical routes to **1** and its corresponding (+)-(2S)-enantiomer **15** were viewed as being directly accessible *via* the chiral imide enolate technology developed independently by the Evans[3] and Oppolzer[4] groups. At the outset it was not clear in what manner the unsaturation (arrow) β to the site of enolate derived from **5** would influence the efficiency of electrophilic substitutions; to the best of our knowledge these type of substrates have not been studied earlier. The wide choice of electrophiles, excellent diastereoselectivities for both alkylations and aldol condensations, and easy access to chiral auxiliaries led us to choose the Evans methodology.[5] We now describe two complimentary routes to **1** using chiral oxazolidinones derived from (S)-valinol and (R)-phenylalaninol respectively.

Synthesis of the desired olefinic acid **7** was accomplished quite simply and in high yields from the allyl alcohol **6** available in bulk from our original chiral epoxide route to **1**.[6] In a one-pot sequence **6** was subjected to Claisen-Johnson orthoester rearrangement[7] with triethyl orthoacetate followed by basic hydrolysis of the resulting ethyl ester to provide **7**

as a crystalline solid, m.p. 65^0 C in 86% yield.[8] Treatment of the acid chloride **8** with the lithium salt of (4S)-(-)-4-isopropyl-2-oxazolidinone according to standard conditions[5] readily provided the chiral imide **5a** in over 80% yield.[8,9] Our first experiments to introduce the benzyloxmethyl funtionality were conducted with the lithium enolate of **5a** using benzyloxymethyl bromide as the alkylating reagent. Although excellent diastereofacial selectivity for the desired benzyl



Reagents: (a) $(EtO)_3C.Me$, EtCOOH (cat.), 120^0; (b) KOH, MeOH, R.T.; (c) **6** Na-salt, oxalyl chloride, 0^{0}C; (d) oxazolidinone Li-salt, THF, -78^{0}C; (e)**4a**, CH_2Cl_2, $TiCl_4$, 0^{0}C, then Et_3N, $BnOCH_2Cl$, 0^{0}C; (f) LAH, THF, 0^{0}C; (g) I_2, MeCN, pyridine, 0-5^{0}C; (h) Na-triazole, DMF, DMPU, 100^{0}C, 24 h; (i) H_2/10% Pd/C; (j) TsCl, pyridine; (k) acetylation; (l) I_2, MeCN;

SCHEME I

ether **9** [10] (over 98:2) was realized, the chemical yields were unacceptably low (~30%). Under these conditions ~40% unchanged **5a** was recovered, plus intractable products. Under the same conditions, saturated substrates have been reported to provide the corresponding benzyl ethers in over 70% yields.[5]

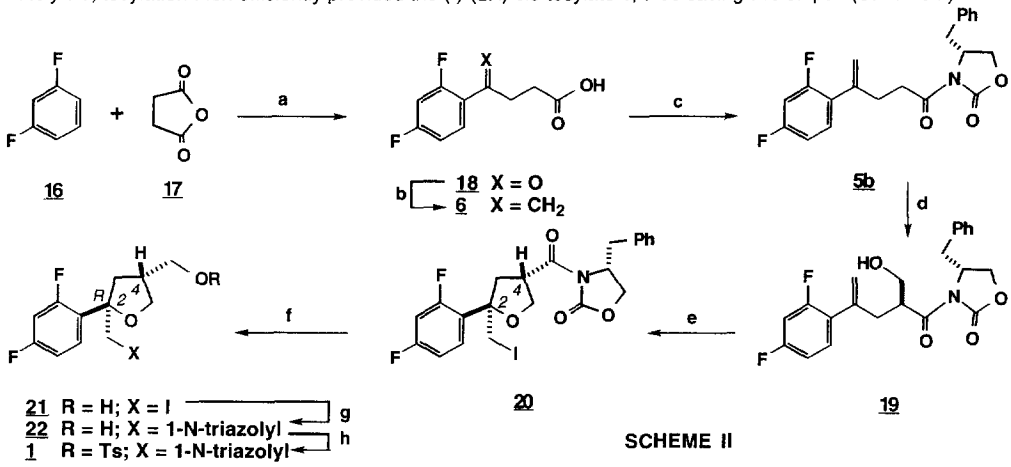
Titanium enolates of N-acyloxazolidinones have been utilized with greatly improved results over Li-enolates in terms of operational simplicity and high diastereofacial selectivity.[11,12] Thus in a marked improvement, alkylation of **5a** with benzyloxymethyl chloride via Evans' titanium enolate protocol[12] gave the benzyl ether **9** in 84% yields (>98% de). No isomerization of the 2,2-disubstituted olefin was detected during either lithium or titanium enolate formation, a requirement crucial to success in this chiral imide route to **1**. Reduction of **9** with LAH in tetrahydrofuran gave the desired (-)-(2S)-diol monobenzyl ether **10**[13] (85% yield) with ~80% recovery of the chiral auxiliary. The remaining steps from iodocyclization onwards proceeded as expected[2] to provide *cis*-1-N-triazolyl benzyl ether **13** and the corresponding *trans*-isomer **13a** (*cis:trans*; >90:10).[14] The undesired **13a** was readily separated from **13** by chromatography. Hydrogenolytic debenzylation of **13** followed by tosylation of the resulting alcohol **14** provided the desired (-)-(2R)-*cis*-tosylate **1**[6] in overall 90% yield and excellent optical purity (>99% e.e.). (Scheme I)

In principle, synthesis of the enantiomeric (+)-(2S)-*cis*-tosylate **15** could be easily carried out by following the above sequence using an appropriate chiral auxlliary such as (4R)-(+)-4-isopropyl-2-oxazolidinone. This was found quite unnecessary as iodocyclization of **11** under the equilibrating conditions according to Rychnovsky and Bartlett[15] provided the iodoacetate of opposite configuration. As we have reported earlier,[2] under these conditions the *'cis:trans'* diastereoselectivity was relatively poor (70:30). However following established conditions, the (+)-(2S)-*cis*-tosylate **15** could be prepared from the major iodocyclization product after chromatographic separation from the minor *trans*-isomer.

The following alternative approach to **1** was undertaken as we were keen to avoid yield limiting protection-deprotection operations. The allyl alcohol **6** we had been using so far was prepared in 4-steps from 1,3-

difluorobenzene.[6] In this manner synthesis of the olefinic acid **7** used above required a total of 6-steps. We were able to synthesize **7** in two simple steps by Friedel-Crafts reaction of m-difluorobenzene with succinic anhydride to provide the crystalline keto acid **18**, m.p. 110°C in over 90% yield. Wittig reaction of **18** in tetrahydrofuran with two equivalents of methylene triphenyl phosphorane then gave the olefinic acid **7** in ~60% yield over 2 steps.

The (R)-phenylalaninol derived chiral imide **5b** was produced in 90% yield by activation of **7** with pivaloyl chloride followed by in-situ reaction of the resulting anhydride with the Li-salt of (4R)-(+)-4-benzyl-2-oxazolidinone.[5] Diastereofacially selective hydroxymethylation of **5b** was best carried out with sym-trioxane using titanium enolate chemistry[12] to provide the aldol product **19** in ~60% yield.[16] The direct iodocyclization of **19** at room temperature with a high degree of diastereoselectivity in favor of the desired *cis*-iodo imide **20** (*cis:trans*, >90:10; 90% yield) is noteworthy.[17] In contrast iodocyclization of **3a** or **10** type substrates required lower temperatures (0-5°C) to achieve the same degree of diastereoselectivity. Lithium borohydride reduction of **20** under controlled conditions followed by chromatography provided the *cis*-iodoalcohol **21**[18] and recovered (4R)-benzyl-2-oxazolidinone in ~90% and 71% yields respectively. As we have noted earlier, displacement of iodine in a neopentyl-like system by the highly nucleophilic triazolyl anion posed no problems.[2] Hydroxyl protection used in our earlier study, proved unnecessary. Indeed direct displacement of iodine in **21** with sodium-triazole according to conditions described earlier,[2] provided the alcohol **22** in 75% yield; tosylation then efficiently provided the (-)-(2R)-*cis*-tosylate **1**, thus saving two steps. (Scheme II)



SCHEME II

Reagents: (a) Friedel-Craft; (b) $Ph_3P{=}CH_2$ (2 equiv.), THF; (c) pivaloyl chloride activation of **6**, oxazolidinone Li-salt, THF, -78°C; (d) **18**, CH_2Cl_2, $TiCl_4$, 0°C, then s-Trioxane, 0°C; (e) I_2, MeCN, pyridine, 0-5°C; (f) $LiBH_4$, THF, -78°C to R.T., 2h; (g) Na-triazole, DMF, DMPU, 100°C, 24 h; (h) TsCl, pyridine.

Notably, no protecting groups were required throughout this entire sequence. This concise new route to **1** offers excellent opportunity for large scale operations. These examples further enhance the scope of Evans' imide enolates as well as the unprecedented 2,4-diastereoselective halocyclizations[2] reported recently.

Based on its superior efficacy and pharmacokinetic profile, **Sch 56592** is in Phase I clinical trials at the present time.[1, 19] We shall report on additional examples of diastereoselective bond constructions with chiral imides of the type **5a** and **5b** in future communications. Further chemistry relating to **Sch 56592** and structure-activity relationships in this series of novel orally active broad-spectrum antifungals will also be reported elsewhere.

Acknowledgements: We would like to cordially thank Professor Ronald Breslow and Sir Derek Barton, FRS for stimulating discussions. We also wish to thank Dr. Birendra Pramanik for mass spectral data and Dr. Mohinder S. Puar for high resolution nmr experiments.

References and Notes:

1. (a) A. K. Saksena, V. M. Girijavallabhan, R. G. Lovey, F. Bennett, R. E. Pike, H. Wang, P. Pinto, Y.T. Liu, N. Patel and A. K. Ganguly, *35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, 17-20 September 1995* (abstract nos. F 61 and F 83); (b) A. K. Saksena, V. M. Girijavallabhan, R. G. Lovey, R. E. Pike, J. A. Desai, A. K. Ganguly, R. S. Hare, D. Loebenberg, A. Cacciapouti and R. M. Parmegiani, *Bioorg. Med. Chem. Lett.*, **1995**, 5, 2023; **Sch 56592:** (-)-4- [4- [4- [[(R-*cis*)-5- (2,4-diflurophenyl)-tetrahydro-5- (1H-1,2,4-triazol-1-ylmethyl)-3-furanyl] methoxy]phenyl]-1-piperazinyl] phenyl]-2,4-dihydro-2- [(S)-1- ethyl-2(S)-hydroxypropyl]-3H-1,2,4-triazol-3-one.
2. A. K. Saksena, V. M. Girijavallabhan, R. G. Lovey, R. E. Pike, H. Wang, A. K. Ganguly, B. Morgan, A. Zaks and M.S. Puar, *Tetrahedron Lett.* **1995**, 36, 1787.
3. Review: D. A. Evans, *Aldrichimica Acta*, **1994**, 15, 23; and cited references.
4. W. Oppolzer, J. Blagg, I. Rodrigues and E. Walther, *J. Am. Chem. Soc.* **1990**, 112, 2767; and cited references.
5. D. A. Evans, M.D. Ennis and D.J. Mathre, *J. Am. Chem. Soc.* **1982**, 104, 1737.
6. A. K. Saksena, V. M. Girijavallabhan, R. G. Lovey, R. E. Pike, J. A. Desai, A. K. Ganguly, R. S. Hare, D. Loebenberg, A. Cacciapouti and R. M. Parmegiani, *Bioorg. Med. Chem. Lett.*, **1994**, 4, 2023.
7. W. S. Johnson, L. Werthmann, W. R. Bartlett, T. T. Brocksom, Tsung-tee Li, D. J. Faulkner, M. R. Peterson, *J. Am. Chem. Soc.* **1990**, 112, 8215.
8. Yields refer to isolated products and have not been optimised. All new compounds were characterised by PMR, CMR and high resolution mass spectra. When necessary diff NOE, COSY and NOESY spectra were obtained. *Cis:trans* ratios of iodocyclization products were determined by NMR as fully described in ref. 2. Where applicable, optical purity of key intermediates was determined by chiral shift NMR spectroscopy. Chiralcel® OD Analytical Columns (Chiral Technologies Inc.) were also used to determine optical purity of a number of final compounds. Selected spectral data is given here.
9. **7**: MS = 213 $(M+H)^+$; ^{1}HNMR [$CDCl_3$] δ 2.48 (t , J = 6.0 Hz , 2H), 2.80 (t , J = 6.0 Hz , 2H), 5.19 (s , 1H), 5.28 (s,1H),6.78 ~ 6.90 (m , 2H), 7.18 ~ 7.30 (m , 1H). **5a**: MS = 324 $(M+H)^+$. ^{1}HNMR [$CDCl_3$] δ 0.90 (dd, J = 6.7 Hz,18.0 Hz, 6H), 2.30 ~ 2.43 (m, 1H), 2.74 ~ 2.90 (m, 2H), 2.95 ~ 3.20 (m, 2H), 4.15 ~ 4.30 (m, 2H), 4.40 ~ 4.47 (m, 1H), 5.20 (s, 1H), 5.30 (s,1H), 6.77 ~ 6.92 (m, 2H), 7.20 ~ 7.30 (m, 1H).
10. **9**: MS = 444 $(M + H)^+$. ^{1}HNMR [$CDCl_3$] δ 0.75 (dd, J = 5.3 Hz, 33.8 Hz, 6H), 2.19 ~ 2.30 (m, 1H), 2.62 (dd, J = 6.0 Hz, 15.0 Hz, 1H), 2.91 (dd, J = 7.5 Hz, 12.8 Hz, 1H), 3.60 (dd, J = 6.0 Hz, 10.5 Hz, 1H), 3.66 (t, J = 7.5 Hz, 1H), 4.12 (m, 2H), 4.31 (m, 2H); 4.43 (dd, J = 12.0 Hz, 18.8 Hz, 2 H), 5.10 (s, 1H); 5.23 (s, 1H), 6.70 ~ 6.85 (m, 2H), 7.09 ~ 7.34 (m, 6H).
11. M. Nerz-Stormes and E.R. Thornton, *Tetrahedron Lett.* **1986**, 27, 897; *J. Org. Chem.* **1991**, 56, 2489.
12. D.A. Evans, F. Urpi, T.C. Somers, J.S. Clark, M.T. Bilodeau, *J. Am. Chem. Soc.* **1990**, 112, 8215.
13. **10**: $[\alpha]_D^{25}$ -28.4° (c = 1.18, $CHCl_3$). MS = 341 (M+Na)$^+$. ^{1}HNMR [$CDCl_3$] δ 1.77 ~ 1.91 (m, 1H), 2.42 (t, J = 4.5 Hz, 1H, exchangeable with D_2O), 2.50 (d, J = 7.5 Hz, 2H), 3.45 (dd, J = 6.8 Hz, 9.0 Hz, 1H), 3.52 ~ 3.75 (m, 3H), 4.46 (dd, J = 7.5 Hz, 13.5 Hz, 2H); 5.17 (s, 1H), 5.23 (s, 1H), 6.73 ~ 6.86 (m, 2H), 7.12 ~ 7.38 (m, 6H).
14. **13** (*cis*-isomer): $[\alpha]_D^{25}$ = - 42.1° (c = 1.17, $CHCl_3$), MS = 386 $(M+H)^+$. ^{1}HNMR [$CDCl_3$] δ 1.90 (m, 1H), 2.42 (m, 2H), 3.17 (dd, J = 6.8 Hz, 9.0 Hz, 1H), 3.28 (dd, J = 6.8 Hz, 9.0 Hz, 1H), 3.66 (dd, J = 7.5 Hz, 9.0 Hz, 1H); 4.04 (t, J = 7.5 Hz, 1H); 4.41 (s, 2H); 4.52 (q, J = 12.8 Hz, 2H), 6.72 ~ 6.86 (m, 2H), 7.21 ~ 7.37 (m, 6H), 7.76 (s, 1H), 8.06 (s, 1H).

    13a (*trans*-isomer): $[\alpha]_D^{25}$ = +10.6° (c = 1.12, $CHCl_3$), MS = 386 $(M+H)^+$. ^{1}HNMR [$CDCl_3$] δ 1.89 ~ 2.0 (m, 1H); 2.06 ~ 2.21 (m, 1H); 2.55 ~ 2.68 (m, 1H); 3.12 (dd, J = 7.5 Hz, 8.2 Hz, 1H); 3.22 (dd, J = 7.5 Hz, 8.2 Hz, 1H); 3.59 (t, J = 7.9 Hz, 1H); 4.06 (dd, J = 7.5 Hz, 8.2 Hz, 1H); 4.34 (s, 2H); 4.50 (d, J = 15.0 Hz, 2H); 6.70 ~ 6.85 (m, 2H); 7.13 ~ 7.40 (m, 6H); 7.80 (s, 1H); 8.05 (s, 1H). **1**: $[\alpha]_D^{25}$ = -39.4° (c = 1.16, $CHCl_3$).[2] **15**: $[\alpha]_D^{25}$ = +37.4° = 1.12, $CHCl_3$)..
15. S. D. Rychnovsky and P. A. Bartlett, *J. Am. Chem. Soc.* **1981**, 103, 3963.
16. **Procedure**: A stirred and cooled (0°C) solution of the chiral imide **5b** (2.18 g, 5.88 mmol) in CH_2Cl_2 (25 ml) was treated with1M $TiCl_4$ (6.5 ml) in CH_2Cl_2. After 5 minutes Hunig's base (1.12 ml) was added and the solution stirred for an additional 30 minutes. A solution of 1,3,5-trioxane (0.67 g, 7.44 mmol) in CH_2Cl_2 (5 ml) was added followed by another 6.5 ml 1M $TiCl_4$ in CH_2Cl_2. The reaction mixture was stirred for 2.5 h at 0°-3°C. Addition of saturated NH_4Cl and extractive work-up gave the crude product. Chromatography on silica gel using 15-25% EtOAc in n-hexane as eluent provided pure **19** (1.33 g).

    5b: $[\alpha]_D^{25}$ = -44.4° (c = 1.67, $CHCl_3$); MS = 371 $(M+H)^+$. ^{1}HNMR [$CDCl_3$] δ 2.74 (dd, J = 9.6 Hz, 13.3 Hz, 1H), 2.82 ~ 3.12 (m, 4H), 3.28 (dd, J = 3.4 Hz, 13.3 Hz, 1H), 4.13 ~ 4.19 (m, 2H), 4.58 ~ 4.71 (m, 1H), 5.20 (s, 1H), 5.31 (m, 1H), 6.74 ~ 7.34 (m, 8H).

    19: [α]D = -62.9° (c = 1.7, $CHCl_3$); MS = 402 $(M+H)^+$. ^{1}HNMR [$CDCl_3$] δ 2.64 ~ 3.01 (m, 3H), 3.24 (dd, J = 3.4 Hz, 13.5 Hz, 1H), 3.77 ~ 3.91 (bs, 2H), 4.0 ~ 4.18 (m, 3H), 4.49 ~ 4.61 (m, 1H), 5.19 (s, 1H), 5.33 (s, 1H); 6.73 ~ 7.4 (m, 8H).
17. **Procedure**: A stirred solution of **19** (1 g, 2.5 mmol) in CH_3CN (20 ml) was treated with pyridine (0.45 ml). After cooling to 0°C iodine (1.78 g) was added allowing the reaction mixture to warm to room temperature. After ~20 h the reaction was quenched with dilute aq. sod sulfite and extracted with Et_2O (2 x 20 ml); the ether extract was dried over $MgSO_4$ and concentrated to dryness in vacuo to provide a residue. Chromatography over silica gel using 50-75% EtOAc in hexane as eluent gave pure iodo-imide **20** (1.2 g). MS = 528 $(M+H)^+$. ^{1}HNMR [$CDCl_3$] δ 2.61 ~ 2.95 (m, 3H), 3.28 (dd, J = 3.4 Hz, 13.3 Hz, 1H), 3.79 (AB quartet, J = 16.7 Hz, 2H), 4.05 ~ 4.33 (m, 5H), 4.65 ~ 4.76 (m, 1H), 6.75 ~ 7.61 (m, 8H).
18. **Procedure**: The iodo-imide **20** (0.9 g) from above was dissolved in THF and the solution cooled to -78°C. A 2M $LiBH_4$ solution in THF (0.85 ml) was then added with stirring while warming to room temperature. After stirring at room temperature for 2 h, the reaction mixture was cooled to -10°C and quenched with saturated NH_4Cl. Evaporation of THF *in vacuo* followed by extractive isolation with CH_2Cl_2 gave the iodo alcohol **21** (0.45 g). Its acetate was identical to the authentic material.[2]
19. *35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, 17-20 September1995* (abstract nos. F 61, F 62, F63, F 64, F 65, F 66, F 67, F 68, and F 83).

(*Received in USA* 24 *April* 1996; *revised* 11 *June* 1996; *accepted* 12 *June* 1996)