Synthesis of a Model System for the Macrocyclic Subunit of the Oximidines

Frank Scheufler, Martin E. Maier*

Universität Tübingen, Institut für Organische Chemie, Auf der Morgenstelle 18, 72076 Tübingen, Germany
Fax (+49) 7071 29 5137; E-mail: martin.e.maier@uni-tuebingen.de

Received 22 May 2001

Abstract: Cross-coupling reaction of aryl triflate **1** and vinyl stannane **13** provided salicylic acid derivative **15**. This compound was converted to the dihydroxy acid **16**, which provided in a size-selective macrolactonization the two macrolides **17** and **18** in a ratio of 60:40. Compound **17** is a model of the macrocyclic core of the oximidines.

Key words: arylations, dihydroxylations, hydrostannations, macrocycles, Stille reaction

The screening of extracts from natural sources for cytotoxic activity is an essential strategy in the discovery process of novel lead structures. An interesting case at hand is a class of macrolides that embrace the oximidines,[1] the salicylihalamides[2-5] and the apicularens.[6-8] Related compounds include the lobatamides[9] and CJ-12,950 (Figure 1).[10] Although these compounds originate from different sources, they nevertheless share common structural features. All of them contain a salicylic acid part, a macrolactone and an enamide side chain. Apicularen differs from the others in that it contains an additional ring, probably being formed through a transannular cyclization. Moreover, these natural products show differences in the number and position of double bonds and the oxidation state of some of the carbon atoms. Comparing the screening profiles of the salicylihalamides with that of other known antitumor compounds indicated that the underlying biological activity might be due to a novel mode of action.

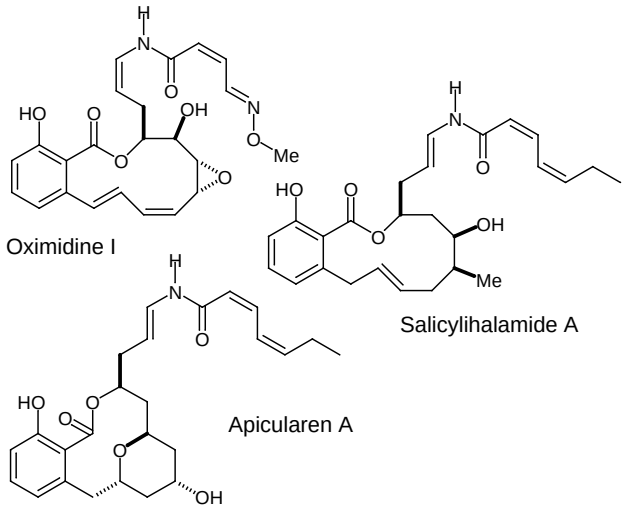


Figure 1

To elucidate the important structural features of these compounds we initiated a program aimed at the synthesis of the natural products and analogs thereof. In this paper we describe initial studies towards the core structure of the oximidines. Retrosynthetic cuts can be made at the enamide,[11] the lactone and the styrene single bond (Figure 2). Initially we targeted a macrocycle lacking the epoxide and the double bond of oximidine I. According to this retrosynthetic analysis and the structural simplification, the aryl triflate **1** and a vinyl stannane, such as **2** became possible starting materials.

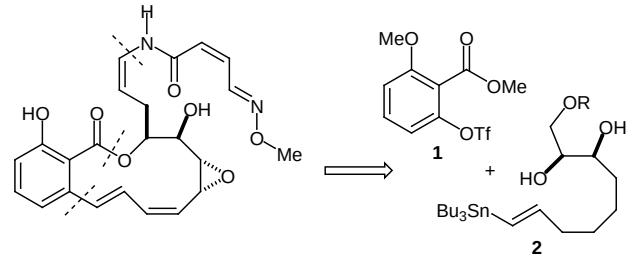
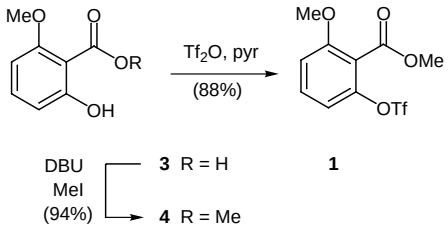


Figure 2

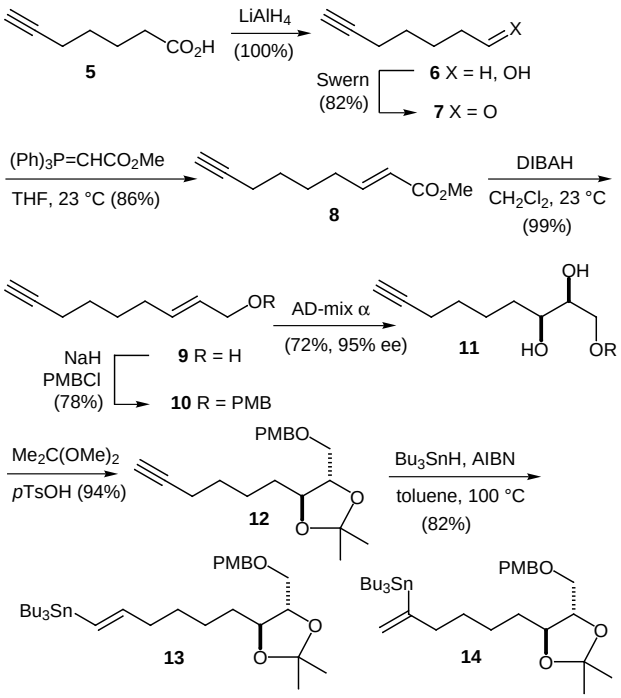
The synthesis began with methyl 2-hydroxy-6-methoxybenzoate **4** which was prepared by esterification[12] (1 equiv DBU, 3 equiv MeI, THF, 0 °C to 23 °C, 19 h) from the commercially available 2-hydroxy-6-methoxybenzoic acid (**3**) (Scheme 1). The hydroxy ester **4** was converted to the triflate in the usual way by treating it with triflic anhydride in the presence of pyridine (1.2 equiv Tf_2O, 23 °C, 20 h).



Scheme 1

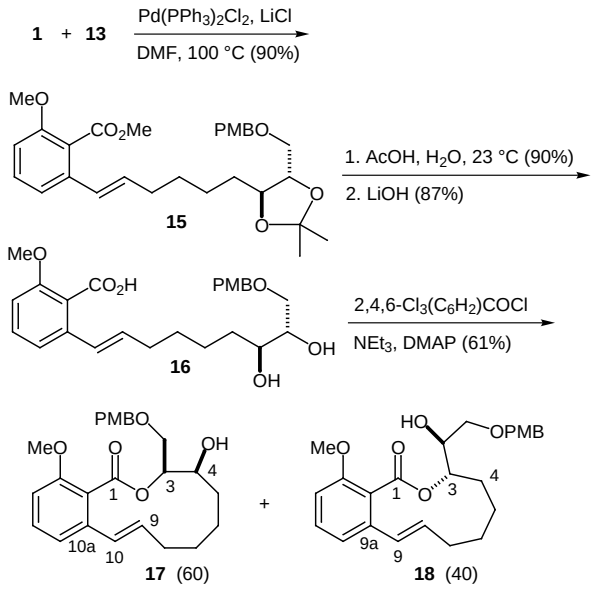
The other building block was built form 6-heptynoic acid (**5**) (Scheme 2). Reduction of **5** to the alcohol **6**, followed by oxidation[13] to the aldehyde and chain elongation by

Wittig reaction with the stabilized ylide (methoxycarbonylmethylene)-triphenylphosphorane (1 equiv, THF, 23 °C, 24 h) gave rise to methyl (2*E*)-2-nonen-8-ynoate (**8**).[14] Reduction of **8** with DIBAH (2.5 equiv, 16 h) gave the allylic alcohol **9**. Next, the hydroxyl group of **9** was protected as its *p*-methoxybenzyl ether **10** (1.5 equiv NaH, 1.0 equiv PMBCl, DMF). The two secondary hydroxy functions could easily be established by a Sharpless asymmetric dihydroxylation reaction [0.004 equiv $K_2OsO_2(OH)_4$, 3.0 equiv $K_3Fe(CN)_6$, 3.0 equiv K_2CO_3, 1.0 equiv $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C, 24 h] using $(DHQ)_2PHAL$ (0.01 equiv) as the chirality inducing ligand (AD-mix α).[15] The enantiomeric excess of **11** ($[\alpha]_D^{25}$ = -14.9 (*c* 1.2, $CHCl_3$)) was determined by chiral HPLC and was found to be 95% [ChiraGrom 2.8 µm, Part-No. GS CH2 0891K0602 (corresponds to CHIRALCEL OD), length: 60 mm, *n*heptane/*i*propanol 95:5, flow: 0.1 mL/min, 284 nm, retention times: 16.2 min (α), 24.5 min (β)]. The next step involved protection of the diol as an acetonide (1.4 equiv $Me_2C(OMe)_2$, 1.5 mol% *p*TsOH, THF, 23 °C, 16 h) to yield compound **12** ($[\alpha]_D^{25}$ = -8.6 (*c* 0.7, $CHCl_3$)). This was followed by addition of tributyltin hydride to the alkyne under radical conditions,[16] which furnished the vinyl stannane **13** as the major addition product (1.1 equiv Bu_3SnH, 0.1 equiv AIBN, toluene, 100 °C, 5 h). Based on ^1H NMR analysis, these conditions provided a 76:24 ratio of the *E*/Z-isomers **13**. This mixture was taken further in the next step. Performing the reaction under palladium catalysis (1.7 equiv *n*Bu_3SnH, 0.02 equiv $Pd(PPh_3)_2Cl_2$, THF, 23 °C, 16 h) gave rise to a mixture of the external and internal stannanes (**13**:**14** = 62:38). In this case however, the stannane **13** was isomerically pure (*E* only).[17]



Scheme 2

A Stille cross-coupling reaction[18] using $Pd(PPh_3)_2Cl_2$ as a catalyst combined the two fragments **1** and **13** (Scheme 3) to provide **15** ($[\alpha]_D^{25}$ = -8.19 (*c* 1.2, $CHCl_3$)) in excellent yield (1 equiv **1**, 1.2 equiv **13**, 0.05 equiv $Pd(PPh_3)_2Cl_2$, 8 equiv LiCl, 0.15 equiv 2,6-di-*tert*-butyl-4-methylphenol, DMF, 100 °C, 18 h). In this context we found that the unprotected diol **2** (R = PMB) gave only low yields in the coupling step. At this stage it was possible to remove the other stereoisomer obtained in the cross-coupling reaction by flash chromatography (petroleum ether/ethyl acetate, 3:1). Liberation of the diol under acidic conditions (80% AcOH, 23 °C, 18 h) followed by basic hydrolysis of the ester group (10 equiv LiOH, THF/MeOH/H_2O (2:2:1), 75 °C, 76 h) delivered the dihydroxy acid **16** ($[\alpha]_D^{25}$ = -8.75 (*c* 0.2, $CHCl_3$)). It was our hope that a size-selective macrolactonization would favor the desired 12-membered lactone. In the event, macrolactonization of **16** under the Yamaguchi conditions[19] (1 equiv 2,4,6-$Cl_3(C_6H_2)COCl$, 1.1 equiv NEt_3, 6 equiv DMAP, toluene, 120 °C, 16 h) gave a mixture of two lactones **17** ($[\alpha]_D^{22}$ = +99.4 (*c* 0.12, $CHCl_3$)) and **18** ($[\alpha]_D^{23}$ = -65.8 (*c* 0.94, $CHCl_3$)) in a ratio of 60:40. These lactones could be separated by preparative HPLC (Grom-SIL 120 Si NP-2, 10 µm, length: 250 mm, *n*heptane/ethyl acetate, 6:4, 10 mL/min, 254 nm).[20] The yield for the macrolactonization was less at higher concentrations (44% at 1.6 mmol/L and 33% at 50 mmol/L).

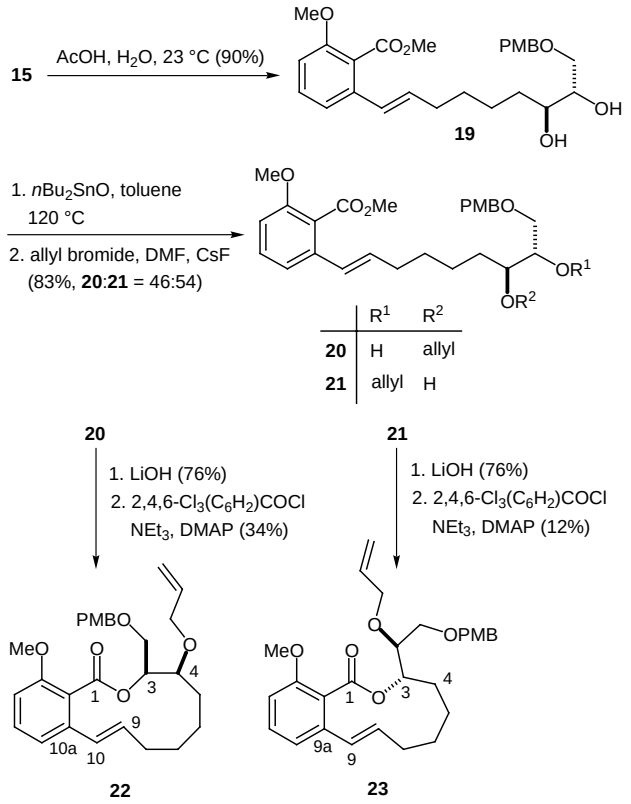


Scheme 3

The structures of the two macrolides were easily distinguished by 2D-NMR spectroscopy. Thus, in the H/H-COSY of macrolide **17**, H-3 (δ = 5.21) shows two crosspeaks with protons that carry an OR function. Specifically, crosspeaks are observed with H-4 (δ = 4.05) and CH_2OPMB (δ = 3.85, 3.77). On the other hand, H-3 (δ = 5.20) of compound **18** is flanked by the cycloaliphatic C-4 methylene group (δ = 1.86, 1.64) and H-1' (exocyc-

lic CHOH, δ = 3.80). These assignments were supported by the H/C-COSY spectra.

The macrolactonization led to a straightforward differentiation of the two secondary hydroxy groups, although with a moderate selectivity. Therefore, we attempted a monoprotection prior to the macrolactonization. In this regard, we took recourse to the corresponding tin acetals.[21] Thus, diol **19**, obtained from **15**, was treated with dibutyltin oxide (1.0 equiv nBu$_2$SnO, toluene, 120 °C, 6 h) in toluene followed by the addition of allyl bromide (1.5 equiv allyl bromide, 2.0 equiv CsF, DMF, 23 °C, 18 h). This reaction gave a 46:54 ratio of the two monoprotected compounds **20** and **21** (Scheme 4). After chromatographic separation each of them was converted to the corresponding hydroxy acid (10 equiv LiOH, THF/MeOH/H$_2$O, 75 °C, 76%). These acids were then subjected separately to the macrolactonization. Again, the Yamaguchi conditions were used. The yields were 34% for the cyclization of **20** to **22** (1.5 mmol/L) and 12% for **21** to **23** (1.3 mmol/L), respectively. The structural assignment was possible at this stage by inspecting the H/H-COSY spectra.



Scheme 4

In summary, we have described a synthesis of the model system for the macrocyclic subunit of the oximidines. Key reactions are the asymmetric dihydroxylation of the enyne **10**, the cross-coupling of the aryl triflate **1** with the vinyl stannane **13** and finally a size-selective macrolactonization of the dihydroxy acid **16**. This study also shows that a macrolactonization can be exploited to differentiate two functional groups. The stripped down ring system will be important to clarify the role of the vinyl epoxide of the oximidines. Studies to incorporate the enamide side chain of salicylihalamide and the oximidines into this model system are underway in our laboratory.

Acknowledgement

Financial support by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* is gratefully acknowledged.

References and Notes

(1) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153.
(2) Isolation: Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188.
(3) Model studies: (a) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731; (b) Feutrill, J. T.; Holloway, G. A.; Hilli, F.; Hügel, H. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2000**, *41*, 8569; (c) Georg, G. I.; Ahn, Y. M.; Blackman, B.; Farokhi, F.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Yang, K. *J. Chem. Soc., Chem. Commun.* **2001**, 255.
(4) First total synthesis and revision of the absolute configuration: Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 4308.
(5) Total syntheses: (a) Wu, Y.; Seguil, O.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241; (b) Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645; (c) Smith, A. B., III; Zheng, J. *Synlett* **2001**, 1019.
(6) Isolation: Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.
(7) Model studies: Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069.
(8) First total synthesis: Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217.
(9) (a) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805; (b) Lobatamide A is identical to the structure of YM-75518, see: Suzumura, K.-i.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R. M.; Suzuki, K.-i.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573.
(10) Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14.
(11) For studies related to the enamide-side chain, see: (a) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407; (b) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397; (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333; (d) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3737.
(12) Mal, D. *Synth. Commun.* **1986**, *16*, 331.
(13) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
(14) Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424.
(15) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(16) (a) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851; (b) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768; (c) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863.
(17) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(18) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *Org. Synth.* **1989**, *68*, 116; (b) Saá, J. M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1992**, *57*, 678; (c) Tsuji, J. *Palladium Reagents and Catalysts - Innovations in Organic Synthesis*; John Wiley & Sons Ltd: Chichester, 1995; (d) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978; (e) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(19) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989; (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.

(20) Macrolactonization: 2,4,6-Trichlorobenzoyl chloride (0.16 mL, 1.0 mmol) was added to a mixture of the hydroxy acid **16** (0.445 g, 1.0 mmol) and triethylamine (0.15 mL, 1.1 mmol) in THF (10 mL), after which the reaction was stirred for 1 h at 23 °C. After removal of triethylamine hydrochloride, the filtrate was diluted with toluene (800 mL) and added to a refluxing solution of DMAP (0.733 g, 6.0 mmol) in toluene (190 mL) over a period of 2 h. After being refluxed for further 16 h, the reaction mixture was diluted with Et_2O (300 mL), washed successively with 3% aqueous HCl, an aqueous $NaHCO_3$ solution, and water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by preparative HPLC (Grom-SIL 120 Si NP-2, 10 μm, *n*-heptane/ethyl acetate, 95:5, 10 mL/min) gave the lactones **17** (157 mg) and **18** (104 mg), combined yield 61%.
17: TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.51 – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27-1.44 (m, 4H, H-5, H-6, H-7), 1.61-1.75 (m, 1H, H-7), 1.78-1.88 (m, 1H, H-5), 2.10-2.31 (m, 2H, H-8), 2.49 (s, br, 1H, OH), 3.71-3.72 (2 s, 1 m, 7H, OCH_3, CH_2OPMB), 3.82 (dd, *J* = 5.8 Hz, *J* = 10.7 Hz, 1H, CH_2OPMB), 3.95-4.02 (m, 1H, H-4), 4.41-4.48 (m, 2H, C*H*$_2$ArOMe), 5.13-5.20 (m, 1H, H-3), 5.69-5.78 (m, 1H, H-9), 6.40 (d, *J* = 15.7 Hz, 1H, H-10), 6.70-6.82 (m, 4H, aromatic H), 7.16-7.23 (m, 3H, aromatic H) – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.80, 23.82, 30.25, 32.50, 55.22, 55.84, 68.61, 70.00, 73.03, 73.23, 109.24, 113.77, 119.98, 122.44, 128.82, 129.34, 130.22, 135.35, 137.98, 156.03, 159.25, 167.70.
18: TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.56 – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07-1.19 (m, 1H, H-6), 1.30-1.68 (m, 4H, H-4, H-5, H-6), 1.75-1.89 (m, 2H, H-4, H-7), 2.25-2.34 (m, 1H, H-7), 2.59 (s, br, 1H, OH), 3.44 (dd, *J* = 6.8 Hz, *J* = 10.0 Hz, 1H, CH_2OPMB), 3.56 (dd, *J* = 3.5 Hz, *J* = 10.0 Hz, 1H, CH_2OPMB), 3.72 (s, 6H, OCH_3), 3.76-3.85 (m, 1H, H-1'), 4.39, 4.47 (2 d, *J* = 11.5 Hz, 1H each, CH_2ArOMe), 5.14-5.19 (m, 1H, H-3), 5.59-5.67 (m, 1H, H-8), 6.33 (d, *J* = 15.9 Hz, 1H, H-9), 6.72-6.82 (m, 4H, aromatic H), 7.16-7.26 (m, 3H, aromatic H) – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.84, 23.56, 28.36, 32.43, 55.22, 55.87, 71.18, 72.26, 73.09, 73.29, 109.38, 113.77, 120.46, 123.06, 129.33, 129.59, 129.99, 130.25, 134.66, 137.96, 156.51, 168.78.

(21) (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643; (b) Qiao, L.; Hu, Y.; Nan, F.; Powis, G.; Kozikowski, A. P. *Org. Lett.* **2000**, *2*, 115.

Article Identifier:
1437-2096,E;2001,0,08,1221,1224,ftx,en;G09501ST.pdf