Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 24, pp. 3091-3096, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00543-9

SYNTHESIS OF APPROPRIATELY FUNCTIONALIZED VANCOMYCIN CD AND DE RING SYSTEMS

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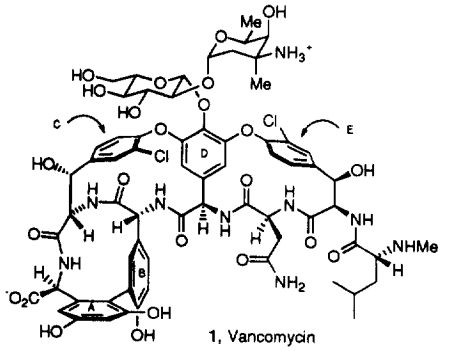
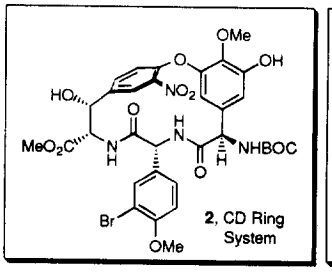
Abstract. Synthesis of appropriately and fully functionalized 16-membered CD and DE ring systems of vancomycin is detailed.

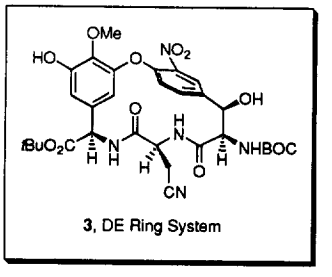
Vancomycin (**1**)[1] was isolated in 1956 from *Streptomyces orientalis* and its structure and stereochemistry were ultimately secured over 25 years later by a combination of chemical degradation,[1b] NMR,[1d,e] and X-ray crystallography studies.[1f] This prototypic member of a large and growing class of clinically effective glycopeptide antibiotics[2-4] which includes teicoplanin,[2a] ristocetin,[2b] β-avoparcin,[2c] actaplanin (A4696),[2d] and A33512B[2e] is characterized by a polycyclic heptapeptide backbone composed of two 16-membered biaryl ether ring systems (CD and DE). Currently, vancomycin is the therapeutic agent of choice for the treatment of Gram-positive bacterial infections caused by methicillin resistant *Staphylococcus aureus* and bacterial infections in patients allergic to β-lactam antibiotics. It is believed to inhibit bacterial cell wall biosynthesis by selectively binding to mucopeptides terminating in the sequence D-Ala-D-Ala.[3,5] Consequently, the binding affinity and selectivity of vancomycin with the C-terminal D-Ala-D-Ala sequence and related cell wall mimics have been the subject of numerous investigations.[3] In addition, the recent emergence of resistant bacteria insensitive to vancomycin has been shown to be the result of transposition of the normal D-Ala-D-Ala peptidoglycan termini of the bacterial cell wall into a depsipeptide D-Ala-D-lactate sequence which itself binds 1000x less effectively with **1**.[6]



1, Vancomycin



2, CD Ring System



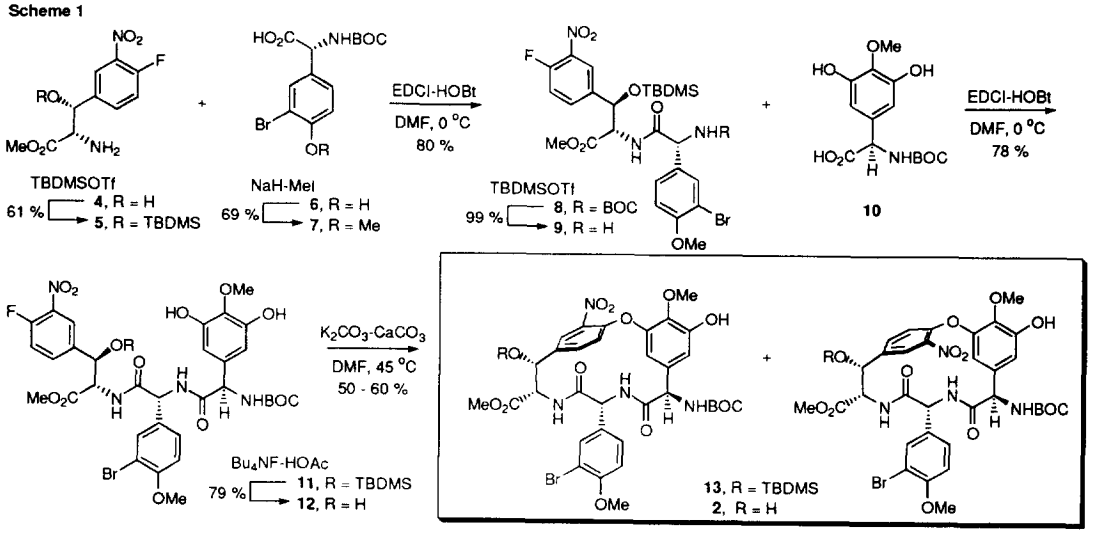
3, DE Ring System

As a result of the structural complexity of the vancomycin family of antibiotics, the interest in defining the fundamental principles underlying the structural basis for its dipeptide binding affinity and selectivity, and issues surrounding the the recent emergence of vancomycin resistance in the clinic, a number of synthetic efforts directed at this family of natural products have been detailed. Efforts from the laboratories of Hamilton,[7] Williams,[8] Yamamura,[9] Evans,[10] Pearson,[11] Brown,[12] Rao,[13] Reddy,[14] Beugelmans,[15] Gallagher,[16] and Danishefsky,[17] as well

as our own[18-20] have addressed aspects of this challenging problem and, to date, no completed total synthesis has been disclosed. With one notable and special exception,[16] previous efforts to prepare the 16-membered CD or DE macrocyclic rings through conventional macrolactamization techniques have been unsuccessful[8] or were found to proceed in low yields.[7,11,12] In the pioneering efforts of Yamamura[9] and Evans,[10] a two-step biomimetic thallium(III)-promoted intramolecular oxidative phenol coupling procedure was used to access a highly functionalized bicyclic species embodying the CDE biaryl ether subunits of vancomycin as symmetrical tetrahalogenated products. In later and complementary efforts, we disclosed the unusually successful implementation of an Ullmann macrocyclization reaction for the preparation of related and more refractory 14-membered biaryl ethers[19] and its surprisingly effective extrapolation to the core 16-membered ring systems of vancomycin.[18] Subsequent to these studies both Beugelmans, Zhu, and coworkers as well as Rao and coworkers have expanded on the scope of such cyclization strategies through use of a nucleophilic substitution of *o*-halonitroaromatics. Initially examined in the intermolecular preparation of vancomycin related biaryl ethers[13,15] as first described by Hamilton,[7] the studies have since been extended to the key intramolecular macrocyclization reaction for formation of 16-membered biaryl ethers based on our Ullmann strategy. We subsequently disclosed the effective synthesis of the cycloisodityrosine 14-membered biaryl ether ring system incorporating the intramolecular nucleophilic substitution reaction of an *o*-fluoronitroaromatic. Herein, we report the results of a study of the extension of these observations to the preparation of the appropriately functionalized 16-membered CD and DE ring systems of vancomycin in which we also disclose a significant technical improvement in the implementation of the methodology.

The CD Ring System. Protection of methyl (2*S*,3*R*)-β-hydroxy-(4-fluoro-3-nitrophenyl)alanine (**4**)[21] as its TBDMS ether **5** (6 eq TBDMOTf, 6.6 eq 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h, 61%) which was isolated as the free amine, $[\alpha]_D^{26}$ -6.1 (*c* 1.1, $CHCl_3$), upon chromatography purification followed by coupling (3 eq EDCI, 3.3 eq HOBt, DMF, 0 °C, 12 h) with (*R*)-N-BOC-(3-bromo-4-methoxyphenyl)glycine (**7**) provided **8** (80%), $[\alpha]_D^{25}$ -55 (*c* 0.7, $CHCl_3$), and a small amount of a separable diastereomer (9%) derived from phenylglycine racemization (Scheme 1). The preparation of **7**, $[\alpha]_D^{26}$ -127 (*c* 0.5, CH_3OH), was most conveniently conducted by direct *O*-methylation (1.9 eq NaH, 1 eq CH_3I, 1:1 THF-DMF, -40 to 0 °C, 3.5 h, 69%) of the free acid **6**,[12] $[\alpha]_D^{26}$ -108 (*c* 0.66, $CHCl_3$), and attempts to prepare **7** from the corresponding methyl ester of **6** suffered substantial racemization upon *O*-methylation and ester hydrolysis. N-BOC deprotection effected by treatment of **8** with TBDMSOTf (2.7 eq, CH_2Cl_2, 0 °C, 1.5 h, 99%) cleanly provided **9**, $[\alpha]_D^{26}$ -25 (*c* 0.4, $CHCl_3$), by a method that precludes *O*-desilylation with no evidence of racemization of the sensitive phenylglycine. Subsequent coupling (3 eq EDCI, 3.3 eq HOBt, DMF, 0 °C, 12 h) of the free amine **9** with (*R*)-N-BOC-(3,5-dihydroxy-4-methoxyphenyl)glycine (**10**)[22] provided **11** (78%) containing less than 5-7% of a diastereomer (≥ 10.5-11:1) derived from epimerization of the intermediate activated carboxylate. TBDMS ether deprotection of **11** (13 eq Bu_4NF, 3 eq HOAc, THF, 25 °C, 12 h, 79%) cleanly provided the alcohol **12**. Comparable deprotections (5 eq Bu_4NF, THF, 25 °C, 3 h) conducted in the absence of added HOAc led to competitive macrocyclization providing both **12** (15%) and **2** (38%, 1:1.7 mixture of atropisomers). Both the alcohol **12** and the TBDMS ether **11** underwent smooth macrocyclization upon treatment

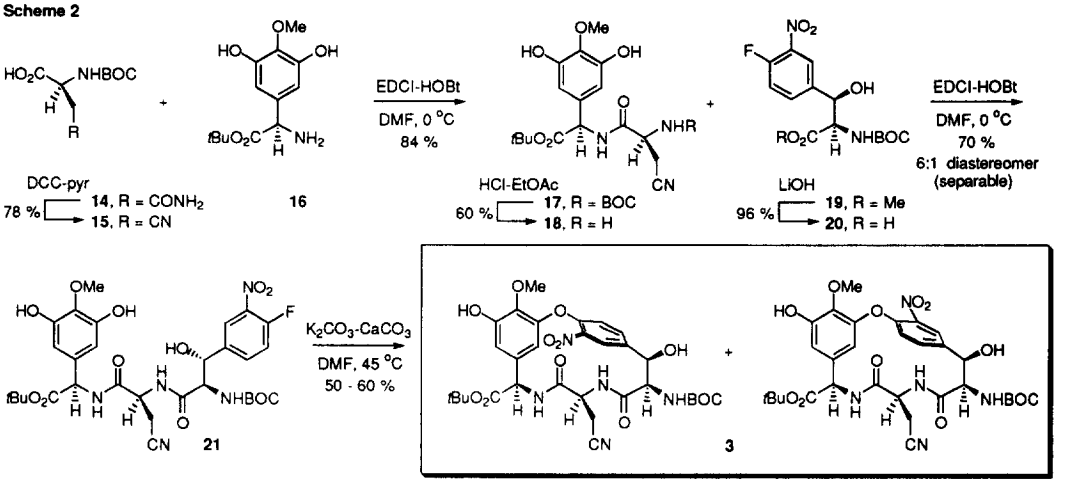
with K_2CO_3-$CaCO_3$ (5 eq, 0.005 M DMF, 45 °C, 12.5 h for **11**, 6 h for **12**) in the presence of 4Å molecular sieves to provide **2** or better **13** (50-60%), respectively, as separable and near 1:1 mixtures of diastereomers.[23] Although this has not yet been examined in detail, macrocyclizations conducted in the presence of 18-crown-6 or in the absence of $CaCO_3$ led to much lower conversions and consumption of the desired cyclization products. Presumably $CaCO_3$ serves as an effective scavenger of the liberated fluoride which is sufficiently basic to promote product decomposition. Consistent with this expectation and in contrast to reactions run in its absence, little TBDMS ether deprotection of **11** was observed to accompany macrocyclization to **13** in the presence of the added $CaCO_3$.



The DE Ring System. Coupling (2 eq EDCI, 1.1 eq HOBt, DMF, 0-25 °C, 16 h, 84%) of L-β-cyanoalanine (**15**),[24] $[\alpha]_D^{23}$ -4.0 (*c* 0.1, CH_3OH), with *t*-butyl (*R*)-(3,5-dihydroxy-4-methoxyphenyl)glycine (**16**),[22] $[\alpha]_D^{23}$ -52 (*c* 0.27, CH_3OH), cleanly provided **17**, $[\alpha]_D^{23}$ -53 (*c* 0.17, CH_3OH), as a single detectable diastereomer (Scheme 2). Acid-catalyzed N-BOC deprotection (1 N HCl-EtOAc, 25 °C, 5 h, 60%) followed by $NaHCO_3$ workup provided **18** as the free base. Hydrolysis (2 eq LiOH, 2:1 *t*BuOH-H_2O, 25 °C, 0.5 h, 96%) of methyl (2*R*,3*R*)-N-BOC-β-hydroxy-(4-fluoro-3-nitrophenyl)alanine **19**,[21] $[\alpha]_D^{23}$ +21 (*c* 0.35, $CHCl_3$), followed by coupling (3 eq EDCI, 1.1 eq HOBt, DMF, 0-25 °C, 14 h, 70%) of **20**, $[\alpha]_D^{23}$ +6.9 (*c* 0.85, CH_3OH), with **18** provided **21**. To date, the best conditions for effecting this coupling has provided a 6:1 mixture of separable diastereomers presumably derived from partial epimerization of the intermediate activated carboxylate. Exposure of **21** to K_2CO_3-$CaCO_3$ (5 eq, 0.005 M DMF, 45 °C, 6 h) cleanly provided **3**[23] as a separable and near 1:1 mixture of diastereomers. In the absence of $CaCO_3$, exposure of **21** to K_2CO_3 (4 eq, 0.008 M DMF) provided recovered starting material (25 °C , 14 h) or lower conversions to **3** (55-60 °C, 3 h, ≤ 10%) with extensive decomposition. In the presence of 18-crown-6, treatment with only K_2CO_3 (10 eq) in THF (25 °C, 0.008 M) provided recovered starting material while reactions in DMF (25 °C) or CH_3CN (55 °C) underwent conversion to multiple products. The TBDMS ether of **21** similarly underwent clean closure to the TBDMS ether of **3** upon treatment with K_2CO_3-$CaCO_3$ (5 eq, 0.005 M DMF, 25 °C,

5 h). With this substrate, the closure occurred under even milder conditions (25 °C vs 45 °C) and the major diastereomer was isolated in yields as high as 40%. Treatment of this substrate with $CaCO_3$ alone (5 eq, DMF, 70 °C, 6.5 h) led to only recovered starting material.

Scheme 2



Thus, the biaryl ether macrocyclization reaction employing the nucleophilic aromatic substitution reaction of *o*-fluoronitroaromatics provided an approach to the construction of an appropriately and fully functionalized vancomycin CD and DE ring system. Efforts to assemble the fully functionalized bicyclic CDE ring system of vancomycin, investigation of the atropisomerism of the resulting agents, and continued investigations on related approaches to the biaryl ether macrocyclization reaction are in progress and will be disclosed in due course.

Acknowledgments. We gratefully acknowledge the financial support of the National Institutes of Health (CA41101) and the award of a NIH postdoctoral fellowship (RMB, GM17548).

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21. Schollkopf, U.; Nozulak, J.; Groth, U. *Synthesis* **1982**, 868. Schollkopf, U.; Nozulak, J.; Grauert, M. *Synthesis* **1985**, 55. For **4**, the relative (2*S*,3*R*)-stereochemistry was established by formation of the cyclic carbamate (J = 5.3 Hz). For **19**, the relative (2*R*,3*R*)-stereochemistry was established by formation of the cyclic carbamate of the free amine (J = 9.0 Hz). For the free amine of **19**: $[\alpha]_D^{23}$ +5.6 (c 0.35, $CHCl_3$). The C2 absolute stereochemistry was established by the absolute stereochemistry of the Schollkopf reagent. **4** has also been prepared by a threonine aldolase catalyzed aldol reaction, Vassilev, V.-P.; Uchiyama, T.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1995**, *36*, 4081, and we thank Wilna J. Moree and Professor C.-H. Wong for providing substantial quantities of **4**.
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23. For **13**: (more polar isomer, R_f = 0.25, 67% EtOAc-hexane) ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.24 (s, 1H, phenol OH), 8.15 (d, 1H, J = 2.1 Hz), 7.93-7.87 (m, 1H), 7.84-7.80 (m, 1H), 7.55-7.45 (m, 2H), 7.41 (d, 1H, J = 8.5 Hz), 7.15 (d, 1H, J = 8.3 Hz), 6.69 (d, 1H, J = 2.0 Hz), 6.42 (d, 1H, J = 2.0 Hz), 6.20-6.10 (m, 2H), 5.62 (s, 1H), 5.48 (d, 1H, J = 7.7 Hz), 5.37-5.30 (m, 1H), 4.68-4.63 (m, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.77 (s, 3H), 1.39 (s, 9H), 0.86 (s, 9H), 0.044 (s, 3H), -0.035 (s, 3H); FABHRMS (NBA-CsI) *m/z* 1021.1331 (M^+ + Cs, $C_{39}H_{49}O_{13}N_4SiBr$ requires 1021.1303). (Less polar isomer, R_f 0.70, 67% EtOAc-hexane) ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.32 (s, 1H, phenol OH), 8.16 (d, 1H, J = 2.1 Hz), 7.68-7.62 (m, 1H), 7.58-7.48

(m, 2H), 7.37 (d, 1H, J = 8.6 Hz), 7.37-7.32 (m, 1H), 7.18 (d, 1H, J = 8.4 Hz), 6.76 (d, 1H, J = 2.2 Hz), 6.68 (d, 1H, J = 2.2 Hz), 6.35-6.25 (m, 1H), 5.90 (d, 1H, J = 8.5 Hz), 5.62 (s, 1H), 5.49 (d, 1H, J = 7.4 Hz), 5.19-5.10 (m, 1H), 4.56 (d, 1H, J = 8.5 Hz), 3.944 (s, 3H), 3.936 (s, 3H), 3.78 (s, 3H), 1.39 (s, 9H), 0.79 (s, 9H), 0.02 (s, 3H), -0.11 (s, 3H), FABHRMS (NBA-CsI) *m/z* 1021.1332 (M^+ + Cs, $C_{39}H_{49}O_{13}N_4SiBr$ 1021.1303). For **2**: (more polar isomer, R_f = 0.50, 56% acetone-hexane) ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.39 (s, 1H), 8.30-8.20 (m, 2H), 7.90-7.75 (m, 2H), 7.68 (d, 1H, J = 2.2 Hz), 7.44 (dd, 1H, J = 8.7, 2.2 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.03 (d, 1H, J = 8.7 Hz), 6.67 (s, 1H), 6.20-6.12 (m, 1H), 5.98-5.88 (m, 1H), 5.72 (s, 1H), 5.60-5.50 (m, 1H), 5.54 (d, 1H, J = 9.0 Hz), 5.31 (d, 1H, J = 9.1 Hz), 5.12-5.06 (m, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 3.75 (s, 3H), 1.39 (s, 9H); FABHRMS (NBA-CsI) *m/z* 907.0464 (M^+ + Cs, $C_{33}H_{35}O_{13}N_4OBr$ requires 907.0438). (Less polar isomer, R_f = 0.55, 56% acetone-hexane) ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.29 (s, 1H, phenol OH), 8.12 (s, 1H), 8.05-7.90 (m, 1H), 7.93 (d, 1H, J = 8.5 Hz), 7.78-7.60 (m, 2H), 7.48 (d, 1H, J = 8.5 Hz), 7.36 (d, 1H, J = 8.5 Hz), 7.06 (d, 1H, J = 8.5 Hz), 6.68 (s, 1H), 6.22-6.13 (m, 1H), 5.93-5.80 (m, 2H), 5.63-5.56 (m, 1H), 5.57 (d, 1H, J = 8.7 Hz), 5.30 (d, 1H, J = 8.6 Hz), 5.03-4.98 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 1.36 (s, 9H); FABHRMS (NBA-CsI) *m/z* 907.0414 (M^+ + Cs, $C_{33}H_{35}O_{13}N_4OBr$ requires 907.0438).

For **3**: (more polar isomer, R_f = 0.31, 5% CH_3OH-$CHCl_3$) ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.42 (s, 1H, phenol OH), 8.21 (d, 1H, NH, J = 8.8 Hz), 8.15 (s, 1H), 7.83 (d, 1H, J = 8.6 Hz), 7.55-7.50 (m, 1H, NH), 7.32 (d, 1H, J = 8.6 Hz), 6.68 (s, 1H), 6.23-6.18 (m, 1H, NH), 5.70 (s, 1H), 5.41 (d, 1H, J = 8.8 Hz), 5.32-5.26 (m, 1H), 5.00-4.96 (m, 1H), 4.75-4.63 (m, 2H), 3.92 (s, 3H), 3.95-3.75 (m, 2H, partially obscured by H_2O), 1.50 (s, 9H), 1.44 (s, 9H); FABHRMS (NBA-CsI) *m/z* 804.1465 (M^+ + Cs, $C_{31}H_{37}N_5O_{12}$ requires 804.1493). (Less polar isomer, R_f = 0.34, 5% CH_3OH-$CHCl_3$) ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.41 (s, 1H, phenol OH), 8.21-8.17 (m, 2H), 7.93 (d, 1H, J = 8.3 Hz), 7.44-7.37 (m, 1H, NH), 7.25 (d, 1H, J = 8.3 Hz), 6.78 (s, 1H), 6.24-6.18 (m, 1H, NH), 5.59 (s, 1H), 5.34-5.32 (m, 1H), 5.26-5.21 (m, 1H), 4.98-4.93 (m, 1H), 4.77-4.69 (m, 2H), 3.96 (s, 3H), 3.95-3.75 (m, 2H, partially obscured by H_2O), 1.46 (s, 9H), 1.44 (s, 9H); FABHRMS (NBA-CsI) *m/z* 804.1471 (M^+ + Cs, $C_{31}H_{37}N_5O_{12}$ requires 804.1493). For the major diastereomer of the TBDMS ether of **3**: ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.41 (s, 1H, phenol OH), 8.18 (d, 1H, NH, J = 8.7 Hz), 8.09 (s, 1H), 7.78 (d, 1H, J = 8.5 Hz), 7.31 (d, 1H, J = 8.5 Hz), 7.19-7.16 (m, 1H, NH), 6.67 (s, 1H), 5.82 (s, 1H), 5.58-5.54 (m, 1H), 5.45 (d, 1H, J = 8.8 Hz), 5.36 (s, 1H), 4.78-4.71 (m, 1H), 4.66-4.59 (m, 1H), 3.92 (s, 3H), 3.96-3.74 (m, 2H, partially obscured by H_2O), 1.51 (s, 9H), 1.46 (s, 9H), 1.00 (s, 9H), 0.20 (s, 3H), -0.05 (s, 3H); FABHRMS (NBA-CsI) *m/z* 918.2319 (M^+ + Cs, $C_{37}H_{51}N_5O_{12}Si$ requires 918.2358).

24. For **14**: Badet, B.; Vermoote, P.; Le Goffic, F. *Biochemistry* **1988**, *27*, 2282. For the dehydration procedure: Liberek, B.; Buczel, Cz.; Grzunka, Z. *Tetrahedron* **1966**, *22*, 2303; Ressler, C.; Ratzkin, H. *J. Org. Chem.* **1961**, *26*, 3356.

(*Received in USA* 16 *November* 1995)