Synthetic Studies towards (–)-Lemonomycin, Synthesis of Fused Tetracycles

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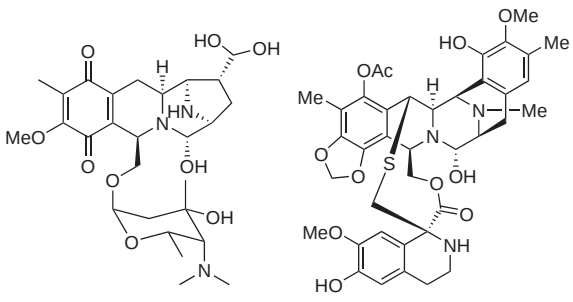
Abstract: The asymmetric synthesis of 1,3-lactol-bridged tetrahydroisoquinoline **5** is developed. Subsequent cyclization of **5** under acidic conditions leads to the formation of a tricyclic enamide **22**, which is in turn converted to a tetracyclic compound **23**.

Key words: amino acid, lemonomycin, tetrahydroisoquinoline, Mannich rection, intramolecular Pictet–Spengler reaction

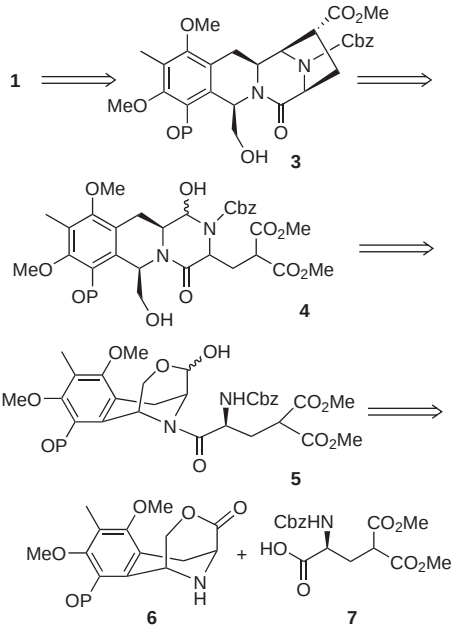
The tetrahydroisoquinoline alkaloids represented by saframycins, ecteinascidins, quinocarcins, tetrazomine and lemonomycin have attracted multidisciplinary interests because of their architectural complexity and potent bioactivities (Figure 1).[1] Lemonomycin (**1**)[2] was isolated for the first time from the fermentation broth of *Streptomyces* (LL-AP191) in 1964, but its structure was elucidated only in 2000 by He and co-workers at Wyeth–Ayerst.[3] Lemonomycin displays interesting antibiotic activities against methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus faecium* (VRE). It is also cytotoxic against a human colon tumor cell line (HCT-116). The broad spectra of antibiotic activities in conjunction with its molecular complexity have made lemonomycin (**1**) an attractive synthetic target. Indeed, Stoltz and co-workers reported the first total synthesis of **1** in 2003,[4] whereas Fukuyama[5] and Magnus[6] reported syntheses of advanced intermediates of **1** in 2005.



Lemonomycin (**1**) Ecteinascidin 743 (**2**)

Figure 1 Structure of lemonomycin (**1**) and ecteinascidin 743 (**2**)

We have been interested in the total synthesis of this class of natural products and have recently accomplished a total synthesis of ecteinascidin 743 (**2**).[7,8] Our planned synthesis of lemonomycin (**1**) featuring a key intramolecular Mannich reaction of **4** is shown in Scheme 1. The 1,3-lactol-bridged tetrahydroisoquinoline **5**, derived from the corresponding lactone, was thought to be a suitable precursor of **4**. Compound **5** could in turn be elaborated from tetrahydroisoquinoline **6** and L-5,5′-dimethyl-*N*-Cbz-4-carboxy-glutamate (**7**).[9] We report herein a successful synthesis of lactol **5** and results of the subsequent cyclization studies.



Scheme 1 Retrosynthetic analysis of lemonomycin (**1**)

Synthesis of L-(2,4-dimethoxy-3-methyl-5-*tert*-butyldimethylsiloxy)phenylalanine *tert*-butyl ester (**12**) is detailed in Scheme 2. Substituted benzyl bromide **9** was synthesized from 2,6-dimethoxytoluene (**8**) following literature procedure.[10] Enantioselective alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester **10** by **9** in the presence of a catalytic amount of *O*-(9)-allyl-*N*-(9′-anthracenylmethyl)cinchonidium bromide (**11**, 0.1 equiv) afforded, after chemoselective hydrolysis of the imine function (THF–H_2O–AcOH), the amino ester **12** in 85% overall yield.[11,12] The *S*-configuration of aminoester **12** was assigned, taking for granted the Corey–Lygo empirical model. To confirm this assignment, both (*S*)-and (*R*)-*O*-methylmandelic acid derivatives **13** and **14** were synthesized (Scheme 2). The calculated chemical shift differences ($\Delta\delta_{ArCH2(\mathbf{13}–\mathbf{14})}$) = –0.05 ppm; ($\Delta\delta_{CO2t\text{-}Bu(\mathbf{13}–\mathbf{14})}$) = 0.10 ppm) are in accord with the *S*-configuration of the amino

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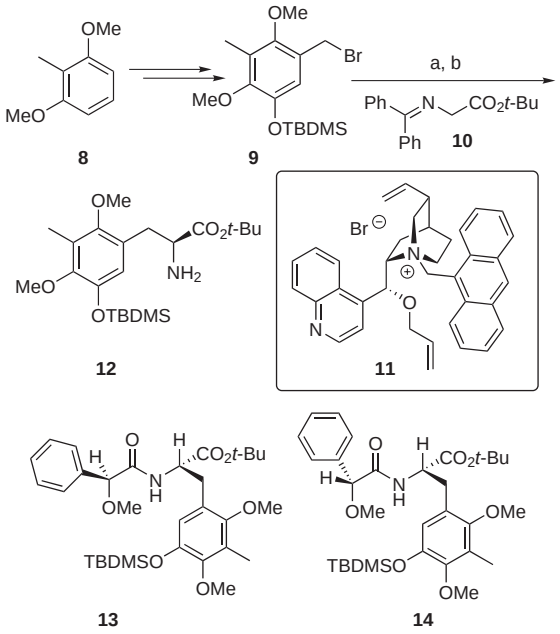
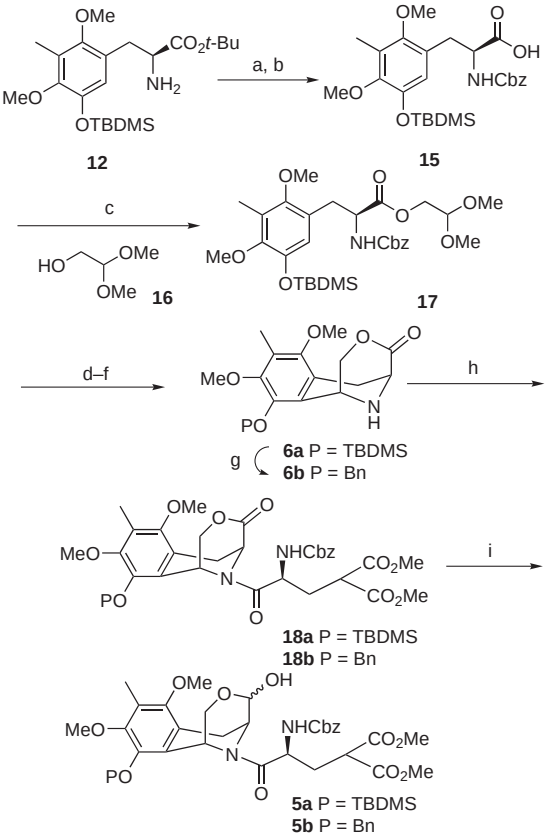


Scheme 2 *Reagents and conditions*: a) **10**, **11** (10%), $CsOH{\cdot}H_2O$, CH_2Cl_2, –78 °C; b) THF–H_2O–AcOH, (1:1:1), 85%.

ester **12**.[13] In addition, analysis of ^1H NMR spectra of compounds **13** and **14** indicated that the de of **13** and **14**, and hence the ee of their precursor **12**, is higher than 90%.

The synthesis of amino lactol **5**, a precursor of aminal **4**, is shown in Scheme 3. N-Protection (CbzOSu, $NaHCO_3$) followed by unmasking of *tert*-butyl ester of **12** under mild acidic conditions (TFA, Et_3SiH) afforded the acid **15**, which was coupled with 2,2-dimethoxy ethanol **16** (EDCI, DMAP) to furnish ester **17** in 83% overall yield from **12**. Chemoselective hydrolysis of the acetal function of **17** ($BF_3{\cdot}OEt_2$, CH_2Cl_2–H_2O) afforded the corresponding aldehyde. Without purification, crude aldehyde was submitted to the optimized conditions for intramolecular Pictet–Spengler reaction (10 equiv of $BF_3{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2) to afford, after removal of the *N*-Cbz function (H_2, Pd/C, EtOAc), the desired tetrahydroisoquinoline **6a** in 90% overall yield. While acetal-deprotection and cyclization sequence can be performed in a one-pot fashion, we found that the overall yield is superior when the two steps were carried out separately. The presence of the bridged lactone unit guaranteed the required 1,3-*cis* stereochemistry.[14] The TBDMS ether **6a** was converted to the benzyl ether **6b** in 87% yield following a standard deprotection (TBAF, THF, 0 °C) and benzylation sequence (NaH, BnBr, DMF). Coupling of **6a** with L-5,5′-dimethyl-*N*-Cbz-4-carboxy-glutamate (**7**, HATU,[15] *i*-Pr_2NEt, DMF, 0 °C) afforded the amide **18a** in 75–85% yield. Chemoselective reduction of lactone **18a** with diisobutylaluminium hydride (DIBAL-H) afforded the corresponding lactol **5a** in 80% yield. Alternatively, the same reduction can be realized with lithium diethoxyaluminium hydride [$LiAlH_2(OEt)_2$, prepared in situ from lithium aluminium hydride and EtOAc] in diethyl ether at –78 °C to provide **5a** in 85–95% yield.[16] Lactol **5b** was synthesized from **6b** following the same synthetic sequence.



Scheme 3 *Reagents and conditions*: a) CbzOSu, dioxane–$NaHCO_3$ sat. H_2O; b) TFA, Et_3SiH, CH_2Cl_2; c) EDCI, DMAP, **16**, CH_2Cl_2, 83% for three steps; d) $BF_3{\cdot}OEt_2$, H_2O, CH_2Cl_2, 0 °C; e) $BF_3{\cdot}OEt_2$, 4 Å molecular sieves, CH_2Cl_2, 0 °C then r.t.; f) H_2, Pd/C, EtOAc, 90% for three steps; g) TBAF, THF, 0 °C, then BnBr, K_2CO_3, DMF, 87%; h) **7**, HATU, *i*-Pr_2NEt, DMF, 0 °C; i) $LiAlH_2(OEt)_2$, Et_2O, –78 °C, 85%.

With lactol **5** in hands, the key intramolecular Mannich reaction for the formation of bridged bicyclic ring system was next investigated (Scheme 4). Following literature precedents dealing with the intramolecular amidoalkylation of malonate,[17] a set of conditions varying the promoters [$TiCl_4{\cdot}Et_3N$, $TiCl_4{\cdot}$pyridine, $TiCl_4$, $SnCl_4$, $AlCl_3$, $Yb(OTf)_3$, TFA, CF_3SO_3H], the solvents (CH_2Cl_2, MeCN), and the temperature (–78 °C, 0 °C, r.t., heating) were examined. Whereas most of these conditions led to the degradation of the starting material, reaction of **5a** mediated by $BF_3{\cdot}OEt_2$ in CH_2Cl_2 provided enamide **22a** in 42% yield. The formation of compounds **22a** could be rationalized as follows. Conversion of lactol **5a** to aminal **4a** followed by dehydration under Lewis acidic conditions would produce the acyliminium intermediate **19a**. The intramolecular nucleophilic addition of malonate onto this electrophilic species would produce the expected product **20**. However, this desired reaction did not take place most probably for unfavorable steric interaction since the enolate of malonate had to attack the iminium from the same face as that occupied by the adjacent C–C bond.[18] Therefore, an alternative iminium–enamine tautomerization would take place to produce enamide **21a** that was further isomerized to afford the conjugated olefin **22a**.[19]

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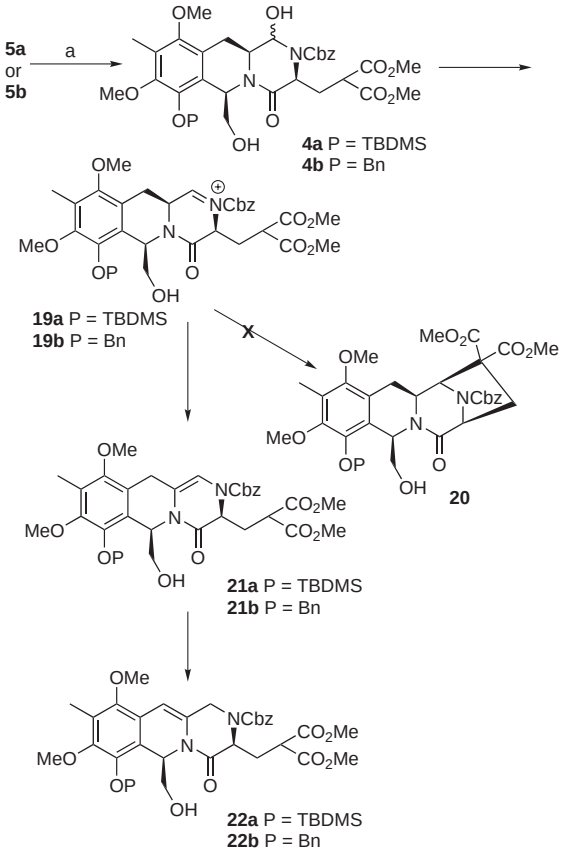
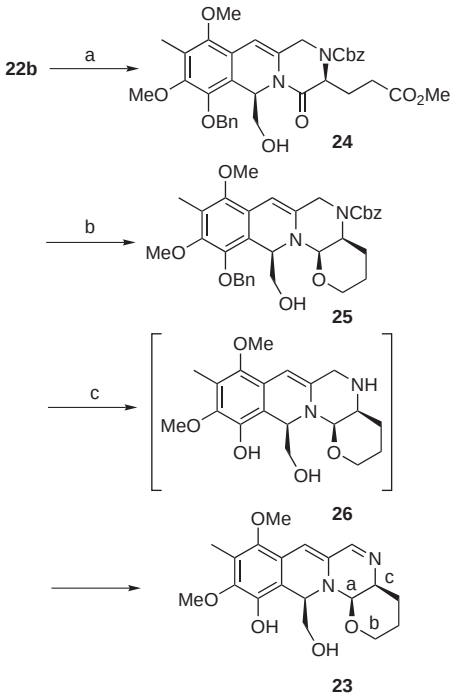


Scheme 4 *Reagents and conditions*: a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, r.t., **22a** (42%); **22b** (40%).



Scheme 5 *Reagents and conditions*: a) LiCl, DMSO–H_2O, 160 °C, 67%; b) $LiAlH_3(OEt)$, Et_2O, 0 °C, 44%; c) H_2, Pd/C, MeOH, 36%.

Compound **22b** was obtained under identical conditions from **5b** in 40% yield.

Taking advantage of the ready availability of **22b**, a tetracyclic compound **23** is synthesized as shown in Scheme 5. Krapcho decarbomethoxylation of **22b** (LiCl in DMSO–H_2O, 160 °C) afforded monoester **24**. Reduction of both ester and amide function with lithium ethoxyaluminium hydride [$LiAlH_3(OEt)$] in diethyl ether at 0 °C provided the aminal **25** in 44% yield. Simultaneous removal of *N*-Cbz and *O*-Bn functions under hydrogenolysis conditions (H_2, Pd/C, MeOH) furnished the secondary amine, which, upon purification (flash chromatograpy, SiO_2), was air-oxidized to provide the conjugated imine **23** in 36% yield. The structure of **23** was fully determined by detailed spectroscopic studies.[20] The observation of C_a–H_b correlation in the HMBC spectrum indicated that a six-membered rather than a five-membered aminal (oxazolidine) was produced, while the coupling constant $J_{Ha–Hc}$ = 2.0 Hz) was indicative of the *cis*-orientation of protons H_a and H_c. The preferred 6-*exo*- over 5-*endo*-addition of alcohol may explain the preferred formation of observed compound **23**.[21]

Compound **23** was inactive against three cancer cell lines (KB, MCF7, MCF7R) tested.

In summary, we have developed an efficient synthesis of highly functionalized 1,3-lactol-bridged tetrahydroisoquinoline **5** and its subsequent transformation to the tetracyclic compound **23**. We are pursuing the total synthesis of lemonomycin by combining **6** with other type of suitably functionalized amino acid building blocks.

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References and Notes

(1) (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (b) Arai, T.; Kubo, A. *The Alkaloids*, Vol. 21; Brossi, A., Ed.; Academic Press: New York, **1983**, 55–100. (c) Fukuyama, T. *Adv. Heterocycl. Nat. Prod. Synth.* **1992**, *2*, 189. (d) Ozturk, T. *The Alkaloids*, Vol. 53; Brossi, A., Ed.; Academic Press: New York, **2000**, 119–238.
(2) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83.
(3) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067.
(4) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000.
(5) Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. *Chem. Commun.* **2005**, 394.
(6) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476.
(7) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87.
(8) For other total syntheses, see: (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.;

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Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2545. (c) For a formal total synthesis, see: Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1754. (d) For a hemisynthesis, see: Cuevas C., Pérez M., Martin M. J., Chicharro J. L., Fernandez-Rivas C., Flores M., Francesch A., Gallego P., Zarzuelo M., De La Calle F., Garcia J., Polanco C., Rodriguez I., Manzanares I.; *Org. Lett.*; **2000**, *2*: 2545.

(9) Couturier, C.; Liron, M.; Schlama, T.; Zhu, J. *Synlett* **2005**, 851.

(10) (a) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353. (b) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745. (c) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (d) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712. (e) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828.

(11) (a) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(12) (a) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.

(13) (a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202. (b) Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 6291.

(14) (a) Kurihara, H.; Mishima, H. *Tetrahedron Lett.* **1982**, *23*, 3639. (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993. (c) Todd, M. H.; Ndubaku, C.; Bartlett, P. A. *J. Org. Chem.* **2002**, *67*, 3985.

(15) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397. (b) Carpino, L. A.; Imazumi, H.; El-Faham, A.; Ferrer, F. J.; Zhang, C.; Lee, Y.; Foxman, B. M.; Henklein, P.; Hanay, C.; Mügge, C.; Wenschuh, H.; Klose, J.; Beyermann, M.; Bienert, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 442.

(16) (a) Brown, H. C.; Shoaf, C. J. *J. Am. Chem. Soc.* **1964**, *86*, 1079. (b) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085. (c) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(17) (a) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065. (b) Malmberg, M.; Nyberg, K. *J. Chem. Soc., Chem. Commun.* **1979**, 167. (c) Kraus, G. A.; Neuenschwander, K. *Tetrahedron Lett.* **1980**, *21*, 3841.

(18) For successful cyclization using enolate chemisty in related system, see ref. 6 and 17a.

(19) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397.

(20) Compound **23**: $[\alpha]_D^{25}$ +37.1 (*c* 0.04, $CHCl_3$). IR ($CHCl_3$): 3623, 3025, 3017, 2975, 2928, 1727, 1455, 1391, 1260, 1201, 1046 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 2.2 Hz, 1 H), 5.87 (s, 1 H), 4.75 (dd, 1 H, *J* = 2.2, 8.5 Hz), 4.46 (d, 1 H, *J* = 2.0 Hz), 3.95 (br d, 1 H, *J* = 11.5 Hz), 3.70 (s, 3 H), 3.68 (m, 1 H), 3.65 (m, 1 H), 3.64 (s, 3 H), 3.45 (m, 1 H), 3.11 (dd, 1 H, *J* = 1.7, 12.1 Hz), 2.41 (br d, 1 H, *J* = 12.1 Hz), 2.14 (s, 3 H), 1.87 (dt, 1 H, *J* = 3.7, 13.1 Hz), 1.82 (m, 1 H), 1.41 (br d, 1 H, *J* = 13.9 Hz) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 159.0, 145.4, 141.0, 130.7, 123.4, 121.8, 100.3, 83.8, 67.3, 62.6, 61.6, 61.1, 57.4, 30.4, 20.5, 9.6 ppm. HRMS (ESI): *m/z* cacld for $C_{19}H_{24}N_2O_5 + H^+$: 361.1763; found: 361.1756.

(21) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

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