Asymmetric Synthesis of 2,4,6-Trideoxy-4-(dimethylamino)-3-*C*-methyl-Llyxohexopyranose (Lemonose)

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Abstract: L-Lemonose, the glycosidic part of (–)-lemonomycin, has been synthesized in ten steps with 18% overall yield from Dthreonine. The key steps are a double, highly diastereoselective Grignard addition to a Weinreb amide and a chemoselective oxidation of a primary alcohol in the presence of a secondary alcohol, a tertiary alcohol and a tertiary amine, leading directly to the lactol.

Key words: sugar, aminosugar, lemonomycin, lemonose tetrahydroisoquinoline

(-)-Lemonomycin (1; Figure 1) was isolated from the fermentation broth of Streptomyces candidus (LL-AP191) in 1964, and its structure was elucidated in 2001 by He and co-workers.¹ The compound contains a complex bridged tetracyclic core belonging to the tetrahydroisoquinoline alkaloid family² and is the only member of this class of alkaloids to possess a carbohydrate linkage. This sugar, 2,4,6-trideoxy-4-(dimethylamino)-3-C-methyl-L-lyxohexopyranose (3; lemonose), has been found in a few other natural products, such as nocathiacin I,³ MJ347-81F4 A,⁴ glycothiohexide α ,⁵ saccharocarcins,⁶ and some of the thiazomycins.⁷ Lemonomycin exhibits potent antibiotic activities against methicillin-resistant Staphylococcus aureus (MRSA), Bacillus subtilis and vancomycin-resistant Enterococcus faecium (VREF). It is also cytotoxic against a human colon tumor cell line (HCT-116). The complex structure, coupled with its remarkable biological activity, has made lemonomycin an attractive target for total synthesis. The synthetic efforts have culminated in one total synthesis by Stoltz⁸ and five syntheses of tetracyclic precursors of lemonomycin by Magnus,⁹ Fukuyama,¹⁰ Williams,¹¹ Mulzer,¹² and by our group.¹³

As part of our program on the synthesis of tetrahydroisoquinoline alkaloids,¹⁴ we initiated a project directed toward the total synthesis of (–)-lemonomycin (1). Our retrosynthetic analysis of 1, shown in Scheme 1, involves late-stage formation of the glycosidic bond between the lemonomycinone amide fragment 2 and lemonose 3. We have recently developed a stereocontrolled synthesis of 2: the aglycon unit of the natural product.¹³ We describe

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Scheme 1 Retrosynthesis of lemonomycin (1)

herein an asymmetric synthesis of **3** using D-threonine as starting material.

Our first approach is shown in Scheme 2. The D-threonine starting material was converted into the Weinreb amide of D-*N*-Boc-*O*-TBS threonine (4) following a standard three-step sequence (Scheme 2). We thought to install the qua-



Scheme 2 Reagents and conditions: (a) Boc_2O , $NaHCO_3$, H_2O , dioxane, r.t., 15 h; (b) $Me(OMe)NH \cdot HCl$, EDCl, NMP, CH_2Cl_2 , -15 °C, 1 h, quant. (2 steps); (c) TBSCl, imidazole, DMF, r.t., 15 h, 99%; (d) MeLi, THF, -40 °C, 45 min, 80%; (e) LDA, EtOAc, THF, -78 °C, 2 h, 86%; (f) TBAF, THF, 0 °C, 3 h, 61%; (g) TFA, CH_2Cl_2 , r.t., 1 h; (h) PhSO₂Cl, DIPEA, CH_2Cl_2 , r.t., 3 h, 43% (2 steps).

ternary carbon centre by two consecutive nucleophilic addition steps. The stereochemical outcome of this sequence was expected to depend on the order of addition and on the transition state that governed the nucleophilic addition to the ketone intermediate. Reaction of 4 with methyllithium provided methyl ketone 5 in 80% yield, which, upon reaction with the lithium enolate of ethyl acetate, afforded 6 as a single diastereomer in 86% yield. Treatment of 6 with tetrabutylammonium fluoride (TBAF) directly afforded the lactone 7 by a sequence of desilylation and lactonization in situ. Compound 7 was subsequently converted into sulfonamide derivative 8 to determine its stereochemistry. Comparison of the NMR data of 8 with those of the lemonose precursor described in Stoltz's synthesis allowed us to conclude that lactone 8, and hence 7, is the C3-epimer of natural lemonose. The absolute configuration of the tertiary alcohol (C3) in 6 is thus (R), resulting from re-face addition of the lithium enolate onto the carbonyl group according to the Cram-chelating model (Figure 1).¹⁵ It is interesting to note that in Stoltz's synthesis, nucleophilic addition of the same nucleophile to the methyl ketone, wherein the vicinal aminoalcohol function was protected in the form of oxazolidine, afforded the opposite stereoisomer according to the Felkin–Ahn model.^{8,16} Attempts to reverse the stereochemical course under a variety of conditions failed.17



Figure 1 Cram chelate-type transition state model accounting for the stereoselectivity observed in product 6



Scheme 3 Reagents and conditions: (a) AllylMgBr, THF, $-78 \,^{\circ}C$, 1 h, 78%; (b) MeMgBr, THF, 0 $^{\circ}C$, 1 h, 44%; (c) O₃, CH₂Cl₂, $-78 \,^{\circ}C$, then NaBH₄, EtOH, H₂O, 50 $^{\circ}C$, 30 min, 81%; (d) TBAF, THF, 0 $^{\circ}C$, 3 h, 76%; (e) anhydrous HCl, MeOH, r.t., 15 h; (f) Formol, NaBH₃CN, AcOH, MeOH, r.t., 8 h, 90% (2 steps); (g) TFA, DMSO, r.t., then IBX, 2 h, 95%.

 Table 1
 Addition of the Methyl Group to Allylketone 9; Optimization of Reaction Parameters^a

Entry	Reagent	Temp (°C)	9/10 (%) ^b	dr (10) ^c
1	MeLi	-78	56:28	4:1
2	MeLi, CeCl ₃	-78	0:88	1:1
3	MeMgBr	-78	84:16	_
4	MeMgBr	0	43:44	>9:1

^a All reactions were run for 1 h.

^b Isolated yield after purification by column chromatography.

^c Ratio estimated by ¹H NMR analysis of the crude material.

Although the synthesis shown in Scheme 2 afforded the C3-epimer of lemonose, the high diastereoselectivity observed in the conversion of methyl ketone 5 into the tertiary alcohol 6 was encouraging. Following the same strategy, we assumed that it might be possible to obtain the desired stereoisomer by simply changing the addition order. This approach is summarized in Scheme 3. Addition of allylmagnesium bromide to the Weinreb amide 4 afforded the allyl ketone 9 in 78% yield. Conversion of ketone 9 into the tertiary alcohol 10 was more difficult than expected. Reaction of 9 with methyllithium gave a poor yield of tertiary alcohol and a large amount of starting material 9 was recovered, likely due to a competitive enolization process (Table 1, entry 1). Use of the organocerium reagent, prepared from MeLi and CeCl₃ in situ,¹⁸ gave 10 in excellent yield, but without any diastereoselectivity (entry 2). The best solution found was to use a Grignard reagent at 0 °C (entry 4). Under these conditions, the desired product 10 was isolated in 44% yield (dr > 9:1) together with 43% of recovered starting material (76% after recycling 9 three times). Ozonolysis of the terminal double bond in 10 with dimethylsulfide as a reducing agent yielded the unstable aldehyde. Alternatively, reduction of the intermediate ozonide by sodium borohydride in ethanol at 50 °C provided alcohol 11 in 81% yield.¹⁹ Subsequent deprotection of the amino group under acidic conditions afforded primary amine 12, which was submitted to the reductive amination step to furnish the dimethylamino derivative 13 in 90% yield over two steps.

If the primary alcohol of aminotriol **13** could be oxidized in a selective manner, this material is potentially one step away from the target aminopyranose **3**.²⁰ Initial attempts to achieve this conversion with hypervalent iodine reagents such as *O*-iodoxybenzoic acid (IBX)²¹ and Dess– Martin periodinane (DMP)²² resulted in complex mixtures. Swern oxidation also failed to give the desired results. Although the presence of tertiary amines is tolerated in hypervalent iodine reagent-mediated oxidation,²³ we suspected that its presence in our case could be problematic.^{21b} Therefore, we decided to temporarily protect the amino function by protonation in situ. Dissolving **13** in dimethylsulfoxide in the presence of trifluoroacetic acid (1.1 equiv) followed by addition of IBX (1.2 equiv) afforded the lactol 3 in 95% yield. The chemoselectivity of this transformation was truly remarkable, since one secondary alcohol, one tertiary alcohol, one tertiary amine, and the resulting lactol function were untouched, providing us with an efficient way to conclude the synthesis without extra protection/deprotection steps.

In summary, we have developed an asymmetric synthesis of lemonose in ten steps with 18% overall yield starting from readily available D-threonine. Key steps involved were (a) a sequential double addition of Grignard reagent to Weinreb amide, creating the quaternary centre with the desired absolute configuration, and (b) one-step conversion of aminotriol **13** into lactol **3** under oxidative conditions. We believe that such a highly chemoselective oxidative protocol will find application in the synthesis of other related systems.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

- (a) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83.
 (b) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067.
- (2) (a) Scott, J. D.; Williams, R. M. Chem. Rev. 2002, 102, 1669. (b) Siengalewicz, P.; Rinner, U.; Mulzer, J. Chem. Soc. Rev. 2008, 37, 2676.
- (3) (a) Constantine, K. L.; Mueller, L.; Huang, S.; Abid, S.; Lam, K. S.; Li, W.; Leet, J. E. J. Am. Chem. Soc. 2002, 124, 7284. (b) Leet, J. E.; Li, W.; Ax, H. A.; Matson, J. A.; Huang, S.; Huang, R.; Cantone, J. L.; Drexler, D.; Dalterio, R. A.; Lam, K. S. J. Antibiot. 2003, 56, 226. (c) Leet, J. E.; Li, W.; Ax, H. A.; Matson, J. A.; Huang, S.; Huang, R.; Cantone, J. L.; Drexler, D.; Dalterio, R. A.; Lam, K. S. J. Antibiot. 2003, 56, 232.
- (4) Sasaki, T.; Otani, T.; Matsumoto, H.; Unemi, N.; Hamada, M.; Takeuchi, T.; Hori, M. J. Antibiot. 1998, 51, 715.
- (5) (a) Steinberg, D. A.; Bernan, V. S.; Montenegro, D. A.; Abbanat, D. R.; Pearce, C. J.; Korshalla, J. D.; Jacobus, N. V.; Petersen, P. J.; Mroczenski-Wildey, M. J.; Maiese, W. M. J. Antibiot. 1994, 47, 887. (b) Northcote, P. T.; Williams, D.; Manning, J. K.; Borders, D. B.; Maiese, W. M.; Lee, M. D. J. Antibiot. 1994, 47, 894. (c) Northcote, P. T.; Siegel, M.; Borders, D. B.; Lee, M. D. J. Antibiot. 1994, 47, 901.
- (6) (a) Horan, A. C.; Shearer, M. C.; Hegde, V.; Beyazova, M. L.; Brodsky, B. C.; King, A.; Berrie, R.; Cardaci, K.; Nimeck, M. *J. Antibiot.* **1997**, *50*, 119. (b) Hegde, V. R.; Patel, M. G.; Das, P. R.; Pramanik, B.; Puar, M. S. J. Antibiot. **1997**, *50*, 126.

- (7) Zhang, C.; Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Zink, D. L.; Occi, J.; Birdsall, G.; Venugopal, J.; Ushio, M.; Burgess, B.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *J. Nat. Prod.* **2009**, *72*, 841.
- (8) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. J. Am. Chem. Soc. 2003, 125, 15000.
- (9) Magnus, P.; Matthews, K. S. J. Am. Chem. Soc. 2005, 127, 12476.
- (10) Rikimaru, K.; Mori, K.; Kan, T.; Fukuyama, T. Chem. Commun. 2005, 394.
- (11) Vincent, G.; Chen, Y.; Lane, J. W.; Williams, R. M. *Heterocycles* 2007, 72, 385.
- (12) Siengalewicz, P.; Brecker, L.; Mulzer, J. Synlett 2008, 2443.
- (13) (a) Wu, Y.-C.; Bernadat, G.; Masson, G.; Couturier, C.; Schlama, T.; Zhu, J. J. Org. Chem. 2009, 74, 2046.
 (b) Couturier, C.; Schlama, T.; Zhu, J. Synlett 2006, 1691.
- (14) For syntheses of other natural products belonging to the same family from our group, see: (a) Wu, Y.-C.; Liron, M.; Zhu, J. J. Am. Chem. Soc. 2008, 130, 7148. (b) Chen, X.; Zhu, J. Angew. Chem. Int. Ed. 2007, 46, 3962. (c) Chen, J.; Chen, X.; Willot, M.; Zhu, J. Angew. Chem. Int. Ed. 2006, 45, 8028. (d) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. J. Am. Chem. Soc. 2006, 128, 87. (e) Chen, X. C.; Chen, J. C.; De Paolis, M.; Zhu, J. J. Org. Chem. 2005, 70, 4397.
- (15) (a) Reetz, M. T.; Hüllmann, M.; Seitz, T. Angew. Chem., Int. Ed. Engl. 1987, 26, 477. (b) Mengel, A.; Reiser, O. Chem. Rev. 1999, 99, 1191.
- (16) (a) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.;
 Rapoport, H. J. Org. Chem. 1985, 50, 325. (b) Evans,
 D. A.; Hu, E.; Tedrow, J. S. Org. Lett. 2001, 3, 3133.
- (17) Selected conditions included: (a) adding HMPT to capture the counter-ion; (b) adding BF₃·OEt₂ to pre-complex the aldehyde, and (c) replacing LDA with KHMDS.
- (18) (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. J. Org. Chem. 1984, 49, 3904. (b) Paquette, L. A. In Encyclopedia of Reagents for Organic Synthesis; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995, 1031. (c) Greeves, N.; Lyford, L. Tetrahedron Lett. 1992, 33, 4759.
- (19) Sousa, J. A.; Bluhm, A. L. J. Org. Chem. 1960, 25, 108.
- (20) For selective oxidation of primary alcohols in the presence of secondary alcoholic groups with IBX, see: Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485.
- (21) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. J. Org. Chem. 1995, 60, 7272. (b) Zhdankin, V. V.; Stang, P. J. Chem. Rev. 2002, 102, 2523. (c) Richardson, R. D.; Zayed, J. M.; Altermann, S.; Smith, D.; Wirth, T. Angew. Chem. Int. Ed. 2007, 46, 6529; and references cited therein. (d) Moorthy, J. N.; Singhal, N.; Senapati, K. Org. Biomol. Chem. 2007, 5, 767. (e) Moorthy, J. N.; Singhal, N.; Senapati, K. Tetrahedron Lett. 2008, 49, 80.
- (22) (a) Dess, D. B.; Martin, J. C. J. Org. Chem. 1983, 48, 4155.
 (b) Dess, D. B.; Martin, J. C. J. Am. Chem. Soc. 1991, 113, 7277. (c) Boeckman, R. K. Jr.; Shao, P.; Mullins, J. J. Org. Synth. 2000, 77, 141.
- (23) (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 4077. (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. J. Am. Chem. Soc. **2004**, *126*, 5192.

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