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Stereocontrolled Synthesis of C1−C17 Fragment of Narasin via a Free Radical-Based Approach

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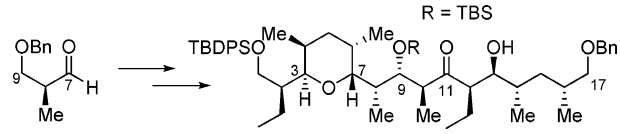
ABSTRACT



An efficient synthesis of the C1−C17 western unit of narasin was achieved from (*S*)-Roche ester. Highlights in our synthesis include the successful exploitation of three stereoselective sequences of Lewis acid mediated reaction followed by free-radical-based hydrogen transfer.

Narasin is produced by *Streptomyces aerofaciens* and was first isolated in 1973 (Figure 1).[1] This complex polyether ionophore is known for its antibacterial and anticoccidal activity.[2] A remarkable total synthesis of this molecule was reported in 1982 by Kishi.[3,4]

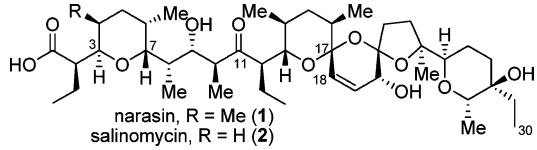


Figure 1. Representative polyethers.

Recently, we reported a versatile methodology for the synthesis of propionate or polypropionate subunits by using a sequence of Mukaiyama aldol and free radical reduction on α-alkyl-β-alkoxy aldehydes, both reactions being controlled by Lewis acid.[5] We have shown that the aldol step could lead to either a 3,4-*syn* or -*anti* relation depending on the presence of a monodentate or a bidentate Lewis acid in the reaction mixture. As seen in Scheme 1A, no efforts were invested to control the stereochemistry of the resulting C2 tertiary bromides, the creation of a free radical being planned in the next step. A mixture tetrasubstituted enoxysilane (*E*/*Z*) was indeed used in these reactions, an interesting characteristic of our strategy. The aldol products could then be reduced to give either the corresponding 2,3-*anti* or 2,3-

(1) Seto, H.; Yahagi, T.; Miyazaki, Y.; Otake, N. *J. Antibiot.* **1977**, *30*, 530.

(2) Ruff, M. D. Veterinary Applications. In *Polyether Antibiotics*; Westley, J. W. , Ed.; M. Dekker: New York, Basel, 1982.

(3) (a) Kishi, Y.; Hatakeyama, S. Lewis, M. D. Total Synthesis of Narasin and Salinomycin. In *Frontiers of Chemistry*; Laidler, K. J., Ed.; Pergamon: Oxford, 1982. (b) Tino, J. A.; Lewis, M. D.; Kishi, Y. *Heterocycles* **1987**, *25*, 97.

(4) There has been considerable effort toward the synthesis of salinomycin: (a) Horita, K.; Nagato, S.; Oikawa, O.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1726. (b) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9. (c) Larossa, I.; Romea, P.; Urpì, F. *Org. Lett.* **2006**, *8*, 527.

(5) (a) Mochirian, P.; Cardinal-David, B.; Guérin, B.; Prévost, M.; Guindon, Y. *Tetrahedron Lett.* **2002**, *43*, 7067. (b) Guindon, Y.; Brazeau, J.-F. *Org. Lett.* **2004**, *6*, 2599. (c) Brazeau, J.-F; Mochirian, P.; Prévost, M.; Guindon, Y. *J. Org. Chem.* **2009**, *74*, 64.

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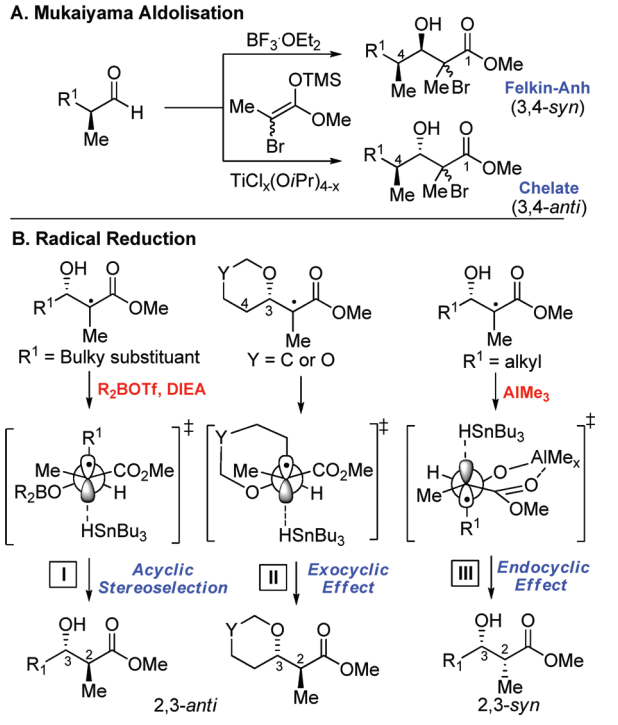
syn isomers (Scheme 1-B). The 2,3-*anti* isomer could be obtained by taking advantage of the acyclic stereoselection (T.S. **I**).[6] A boron-based Lewis acid (Bu_2BOTf) and DIEA were used in this case to create a borinate that serves as a temporary protecting group. Minimization of both the 1,3-allylic strain and the intramolecular dipole−dipole interactions are at the origin of the preferred transition state **I**. However, when R^1 bears a methylene group at C4, the ratio may be lowered. We found that the diastereoselectivity could be enhanced by creating a ring α to the carbon-centered free radical (T.S. **II**, exocyclic effect).[7] Finally, a 2,3-*syn* relative stereochemistry could also be induced by adding a bidentate Lewis acid ($AlMe_3$) to the reaction mixture. The radical center is now embedded in a temporary ring, and the diastereoselectivity is resulting from T.S. **III** (endocyclic effect).[8]

Scheme 1. Substrate-Controlled Strategies with Mukaiyama Aldol Reactions and Radical Reductions



Our objective in the present study was to investigate the robustness of these reactions in the synthesis of various polyether ionophores containing polypropionate subunits, including a fragment of narasin (**1**), on which we are reporting herein.[9] Our retrosynthetic analysis of the western fragment of narasin is illustrated in Scheme 2.

The first disconnection planned is between C12 and C13.[10] An *anti*-Felkin aldol reaction between the aldehyde **5**[11] and the corresponding ketone **4** would be required.[12] This ketone would in turn originate from the aldehyde **6** reacting with enoxysilane **7**. The 8,9-*syn* relative stereochemistry indicates that a monodentate Lewis acid be used in the aldol step and that the radical reduction under the acyclic stereoselection be performed to access the 9,10-*anti* relation. The 2,3-*anti* stereochemistry in tetrahydropyran **6** would come from the reduction of the carbon-centered radical at C2 under the exocyclic effect. The tertiary bromide, precursors of the radical intermediate, would be the products of the addition of enoxysilane **8** on the cyclic oxonium derived from acetal **10**, a 3,7-*anti* relative stereochemistry being sought after. The acetal, in turn, would originate from the coupling of the iodide **11** via Myers' alkylation.[13] Finally, this primary halide would come from the transformation of the 2,3-*syn*-3,4-*anti* stereotriad derived from a sequence of Cram-chelated Mukaiyama aldolisation and a free radical hydrogen transfer using starting material **12**.

Our synthesis began with a titanium-mediated Mukaiyama aldol reaction under chelation control using the tetrasubstituted enoxysilane **7** and aldehyde **12** derived from (*S*)-Roche ester (Scheme 3). The *β*-hydroxy esters having a tertiary bromide at C2 were isolated in good yield and excellent 3,4-*anti* selectivity. These products were treated with $AlMe_3$ (3 equiv) in CH_2Cl_2 at −78 °C before tributyltin hydride (Bu_3SnH) was added and the free radical cascade was initiated with Et_3B in presence of air. The desired 2,3-*syn*-3,4-*anti* propionate **13** was isolated in good yield with high diastereoselectivity.[14] The hydroxyl at C3 was protected using TESOTf and 2,6-lutidine followed by reduction to the primary alcohol **14** in almost quantitative yield. The alcohol **14** was then transformed into the sensitive iodide **11** using Corey's procedure.[15] The subsequent Myers' alkylation was performed by adding the primary iodide to the enolate derived from the corresponding amide containing (*S*,*S*)-pseudoephedrine. Excellent stereoselectivity was obtained, and the diastereoisomer **15** was isolated (dr >20:1, 91%).[16] The amide was refluxed under acidic conditions (PPTS) in benzene to give lactone **16** in good yield without any noticeable epimerization. Reduction of the lactone with DIBAL-H at −78 °C led to the lactol that was transformed to the corresponding acetals (**10a** or **10b**).

(6) (a) Guindon, Y.; Jung, G.; Guérin, B.; Ogilvie, W. W. *Synlett* **1998**, *3*, 213. (b) Cardinal-David, B.; Brazeau, J.-F.; Katsoulis, I. A.; Guindon, Y. *Curr. Org. Chem.* **2006**, *10*, 1939.

(7) Guindon, Y.; Faucher, A.-M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276.

(8) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6566.

(9) For a review on polyether ionophores, see: Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.

(10) Precedents from Evans suggest the stereodifferentiation between those to be fully matched. See: (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpì, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.

(11) Compound **5** was obtained by oxidation of the corresponding known alcohol (96%). See: Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003**, *5*, 1617.

(12) In previous works towards the synthesis of narasin and salinomycin, the C9−C10 bond was generated by an *anti* aldol reaction with moderate stereoselectivities. See ref 4.

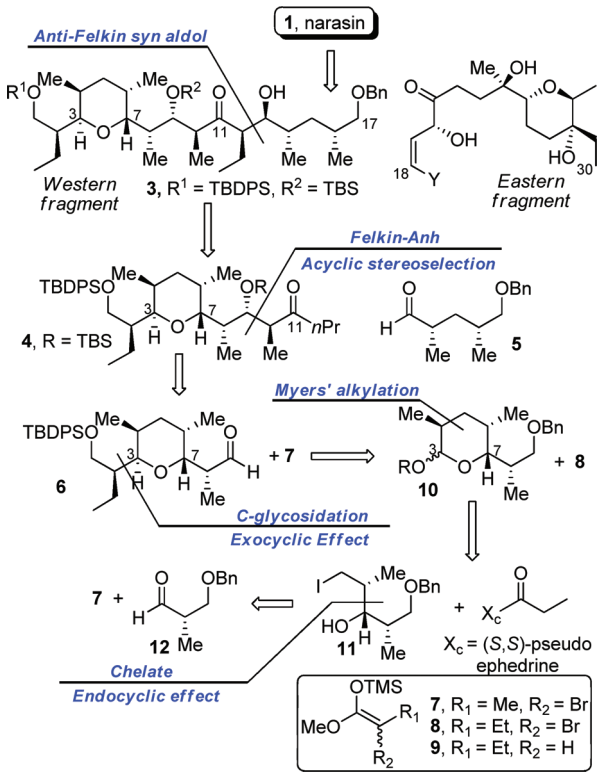
(13) Myers, A. M.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(14) Guindon, Y.; Houde, K.; Prévost, M.; Cardinal-David, B.; Landry, S. R.; Daoust, B.; Bencheqroun, M.; Guérin, B. *J. Am. Chem. Soc.* **2001**, *123*, 8496.

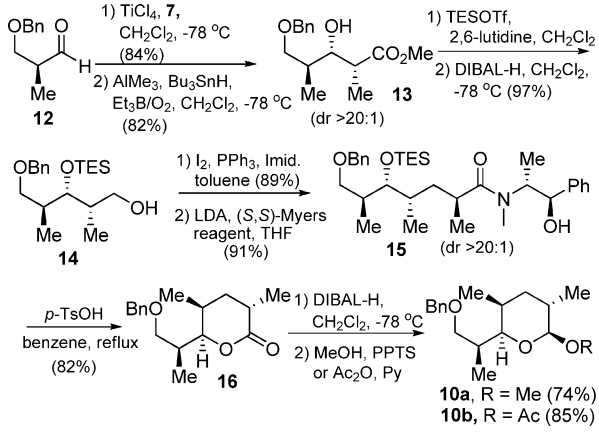
(15) Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883.

(16) At this stage, the presence of amide rotamers complicated the determination of the diastereoselectivity of the newly formed stereocenter. The dr was determined after cleavage of the pseudoephedrine moiety.

Scheme 2. Retrosynthetic Analysis

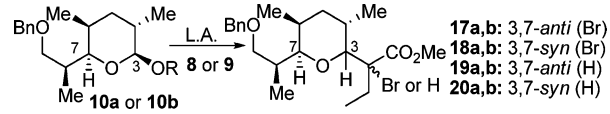


Scheme 3. Synthesis of Acetals **10a** and **10b**



To address the challenge of constructing the less thermodynamically favorable *trans* pyran, an approach based on a Lewis acid catalyzed condensation of an acetal derivative with enoxysilane **8** that bear a carbon-bromide bond was explored (Table 1).[17,18] Treatment of the β-methoxy acetal **10a** with $BF_3{\cdot}OEt_2$ (entry 1) and $TiCl_4$ (entry 2) led to a complex mixture of products, the elimination product (glycal) being the major one. The β-acetal **10b** was then studied, and treatment at −78 °C with $BF_3{\cdot}OEt_2$ gave also disappointing results (entry 3). Our first positive results came from the pretreatment of **10b** with $TiCl_4$ followed by addition of enoxysilane **8**. A significant yield of aldol products was obtained albeit with no diastereoselectivity (entry 4). Fortunately, changing to tin-based Lewis acids led to exciting results. The 3,7-*anti* products **17a,b** were obtained selectively, and not surprisingly, epimers at C2 were noted (entry 5). Similar results were noted with $SnBr_4$ (entry 6). Interestingly, switching **8** for enoxysilane **9** (6:1 ratio), in which the bromide is replaced by a hydrogen, gave also a diastereoselective reaction at C3 (3,7-*anti*) and a mixture of isomers at C2 (entry 7).

Table 1. Optimization of Reaction Conditions for the Lewis Acid Catalyzed Mukaiyama Aldol Reaction



entry[a]	substrate	enoxysilane	Lewis acid	3,7-*anti*: 3,7-*syn* products	3,7-*anti*: 3,7-*syn* ratio[b]	yield[c] (%)
1	**10a**, R = Me	**8**	BF_3OEt_2	**17a,b**:**18a,b**	nd	0[d]
2	**10a**, R = Me	**8**	$TiCl_4$	**17a,b**:**18a,b**	nd	0[d]
3	**10b**, R = Ac	**8**	BF_3OEt_2	**17a,b**:**18a,b**	nd	nd
4	**10b**, R = Ac	**8**	$TiCl_4$	**17a,b**:**18a,b**	1:1	57
5	**10b**, R = Ac	**8**	$SnCl_4$	**17a,b**:**18a,b**	>20:1[e]	83
6	**10b**, R = Ac	**8**	$SnBr_4$	**17a,b**:**18a,b**	>20:1[e]	72
7	**10b**, R = Ac	**9**	$SnCl_4$	**19a,b**:**20a,b**	>20:1[f]	84

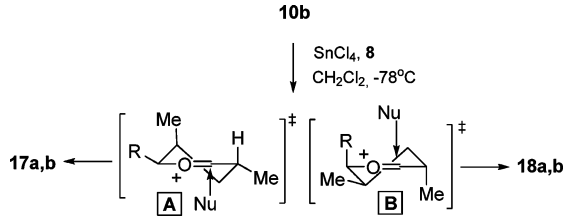
[a] Reaction conditions: Acetal **10a** or **10b** (0.1 M) in CH_2Cl_2 was precomplexed at −78 °C with the appropriate Lewis acid followed by addition of enoxysilane (1.3 equiv). [b] Ratios were determined by ^1H NMR spectroscopy. [c] Yields of isolated products. [d] Elimination product was observed as the major product. [e] 1:1 ratio of bromides **17a**:**17b** was observed [f] 1:1 ratio of esters **19a**:**19b** was observed.

Our mechanistic rationale is based on the formation of the cyclic oxonium ion from **10b** as depicted in Scheme 4.[19] An axial attack of the nucleophile on the oxocarbenium was postulated for stereoelectronic reason.[20] The presence of a sterically encumbered substituent at C3 should be of significant importance for the diastereoselectivity of this reaction. Therefore, minimization of the steric interactions between the incoming nucleophile (**8**) and the R chain should favor transition state **A** leading to the 3,7-*anti* products **17a,b**. More has to be done both experimentally and theoretically to fully determine the reaction mechanism of this transformation.[21]

With tertiary bromides **17a,b** in hand, we then turned our attention to the free radical hydrogen transfer (Scheme 5).

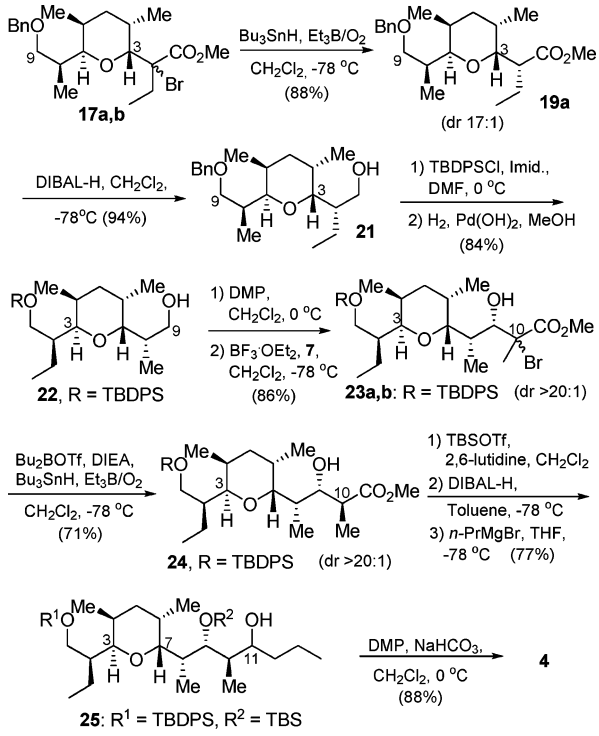
(17) Holmes, C. P.; Bartlett, P. A. *J. Org. Chem.* **1989**, *54*, 98.
(18) Lewis, M. D.; Cha, J. D.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
(19) Only the conformers of the chair-like T.S. are considered as the kinetically controlled reaction should not favor the attack that proceeds through the boat-like T.S.
(20) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E. , Ed.; Pergamon Press: Oxford, 1983.
(21) For recent studies related to nucleophilic substitutions of tetrahydropyran acetals, see: Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 8039, and references therein.

Scheme 4. Proposed Transition States



This reaction was achieved with high yield (91%) and excellent diastereoselectivity (dr 17:1) to give the 2,3-*anti* desired product (**19a**).[22] Then, reduction of ester **19a** led to **21** with good yield (94%).

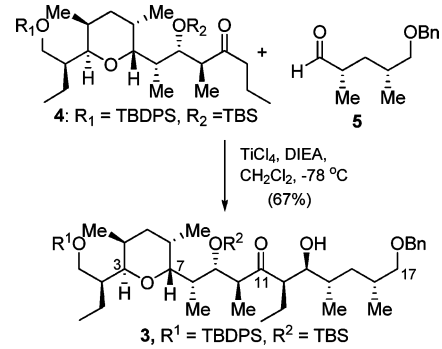
Scheme 5. Synthesis of **4**



A sequence of protection with TBDPS and debenzylation furnished the desired alcohol **22**. The latter was oxidized to aldehyde **6**, which was treated immediately with $BF_3{\cdot}OEt_2$ and enoxysilane **7** to give exclusively the aldol products **23a,b** with a 8,9-*syn* relative stereochemistry. The monodentate activation suggests a Felkin−Anh pathway to selectively form the 8,9-*syn* radical precursors (dr >20:1). The 9,10-*anti* stereochemistry was finally established by treatment of **23a,b** with Bu_2BOTf, DIEA, and Bu_3SnH. This procedure led exclusively to **24** with all the desired stereocenters in place (dr > 20:1).[22] The resulting ester was protected (TBSOTf) and reduced (DIBAL-H) to the aldehyde. Propynylmagnesium bromide was directly added to the nonpurified aldehyde to avoid racemisation. Oxidation using Dess−Martin periodinane[23] afforded the desired ketone **4** with good yield (88%).

As illustrated in Scheme 6, the final coupling involved a *syn*-aldol reaction with aldehyde **5** to give the C1−C17 western fragment of narasin (dr >20:1).[22] The enantiomerically pure unit **3** was isolated in 67% yield along with unreacted ketone starting material **4** (15%).

Scheme 6. Final Step



In conclusion, we have described here a stereoselective synthesis of the western subunit of narasin in 21 steps from aldehyde **12** (7.5% overall yield). The synthetic sequence features three key stereoselective Lewis acid activated addition reactions followed by efficient hydrogen transfer reductions. Efforts are now underway to construct narasin and other natural products of this family.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902414U

(22) See Supporting Information for details that provide proof of stereochemical assignments.

(23) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.