A NEW, EFFICIENT SYNTHESIS OF THE LEFT HALF OF NARASIN[1]

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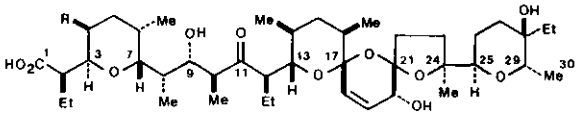
Abstract - The coupling of the acetates 15a,b or 17a,b with the enol silyl ether 19 in the presence of $ZnCl_2$ was shown to yield exclusively the desired C.7 axial products. The stereoselectivity at the C.8 position was about 3.5:1 favoring the natural configuration.

Earlier work in our laboratories led to the first total synthesis of polyether antibiotics narasin (1a) and salinomycin (1b).[2,3] A key step in this synthesis was a stereospecific

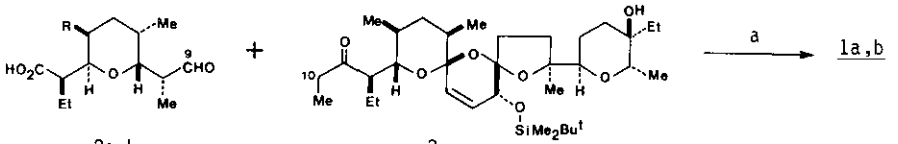


1a : Narasin (R=Me)

1b : Salinomycin (R=H)

crossed aldol reaction such as 2a,b + 3 → 1a,b (Scheme 1). The synthesis of the right half ketone 3 was effectively executed as planned. However, the synthesis of the left half aldehyde 2, particularly in the narasin series, did present a problem. In this communication, we would like to report a new, efficient route to the aldehyde 2a.

Scheme 1



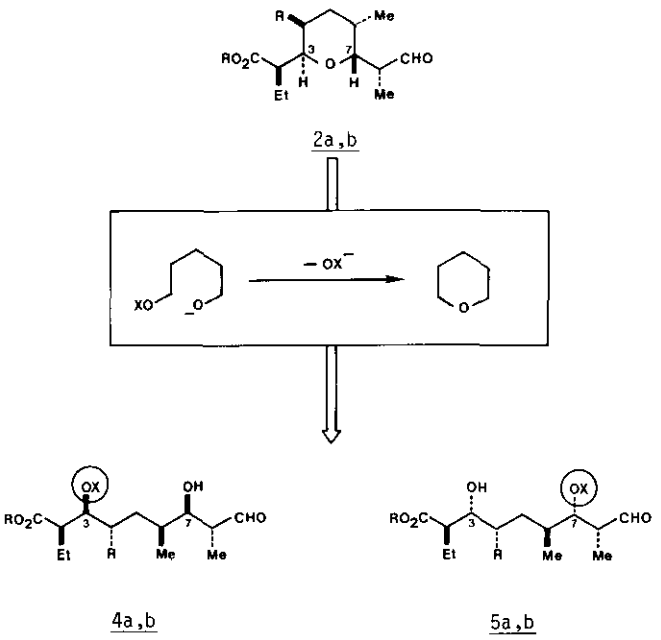
2a,b 3

Reagents and conditions

a. 1. anion formation of 3 : 3/(c-hex)$_2$NMgBr/THF/-50°C. 2. Addition of 2 into the anion solution of 3 : THF/-50°C. 3. (n-Bu)$_4$NF/THF/RT. 4. TFA/CH_2Cl_2/4Å molecular sieves/RT.

We originally planned to construct the tetrahydropyran ring of 2 from a suitably functionalized 1,5-diol by an S_N2 displacement reaction as depicted in Scheme 2. Of the two possible precursors 4a,b and 5a,b, the aldehydes 4a,b were chosen due to their structural similarity to the C.11-C.17 moiety of narasin and salinomycin.[2] Conformational analysis of the narasin aldehyde 2a indicates that the proposed cyclization may be troublesome. The narasin

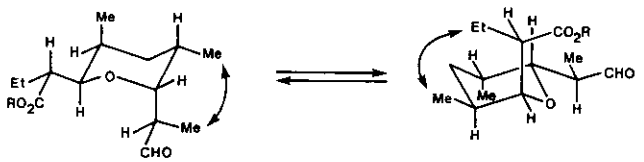
Scheme 2



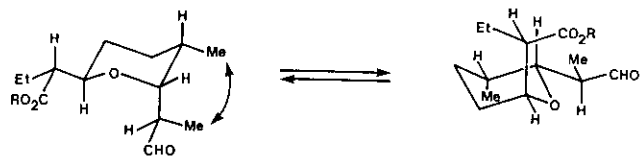
4a,b 5a,b

aldehyde 2a is a sterically crowded molecule; serious steric compressions exist in both conformations 2a-A and 2a-B[4] due to the two axial substituents and also due to the interaction between the branched axial substituent and the methyl group.[5] Thus, the transition state leading to 2a is considered also sterically crowded. Similar analysis suggests that the salinomycin aldehyde 2b is sterically crowded but not as extensively as the narasin aldehyde 2a - compare 2b-A ⇄ 2b-B with 2a-A ⇄ 2a-B. Thus, the cyclization leading to 2b may not be as difficult as that to 2a. Nevertheless, hoping that the intramolecular nature of the displacement might offset the obvious steric problems, cyclizations of two key substrates 6a and 6b were examined in detail.

Scheme 3



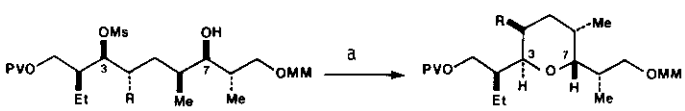
2a-A 2a-B



2b-A 2b-B

Cyclization was attempted under a variety of conditions. Only in very nonpolar solvent systems was the desired tetrahydropyran formed to any appreciable extent. When a suitably activated substrate such as 6a was subjected to the classical conditions favoring S_N2 reaction with uncharged electrophiles, i.e., polar aprotic solvents, only elimination was observed. The best cyclization conditions entailed dissolving substrates with a small amount of 18-crown-6 in a mixture of hexanes and toluene, followed by addition of oil-free KH at 0°C. In this manner, the desired tetrahydropyran 7b could be isolated in 59% yield in the salinomycin series. However, in narasin series the desired tetrahydropyran 7a was obtained only in 14% yield even under the best conditions; the major products (66% yield) were olefins derived from elimination.

Scheme 4



6a,b 7a,b

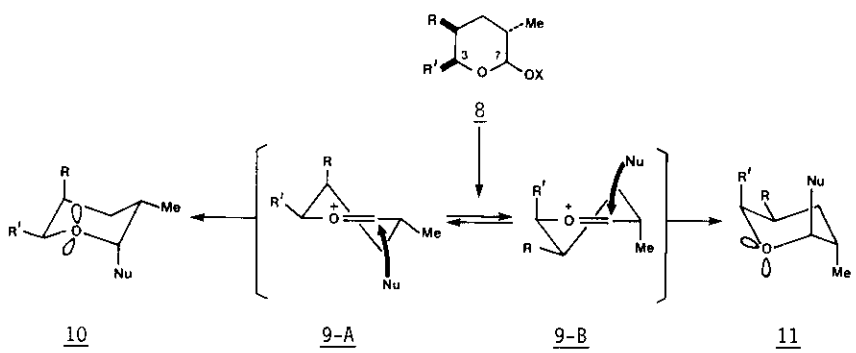
PV=$(Me)_3CCO$-, MM=$MeOCH_2$-

Reagents and conditions

a. KH (oil free)/18-crown-6/toluene-hexanes (1/1)/0°C.

In light of these results, a more efficient synthesis of the narasin aldehyde 2a was investigated. Since the formation of the fully substituted tetrahydropyran via S_N2 displacement proved to be difficult, the stereocontrolled addition of an alkyl group to a preformed tetrahydropyran nucleus was pursued; in particular, we were interested in applying the stereocontrolled C-glycosidation reaction developed in our laboratories to this case (Scheme 5).[6] Namely, we anticipated that the carbon-carbon bond formation would preferentially take place from the axial direction on the conformer 9-A of the oxonium ion to yield the desired product 10 on the basis of (1) the stereoelectronic effect, i.e. the C-Nu bond is antiperiplanar to one of the lone pair electrons of oxygen in 10 and 11, and (2) the steric hindrance due to the R' group in the conformer 9-B for the incoming nucleophile.[7]

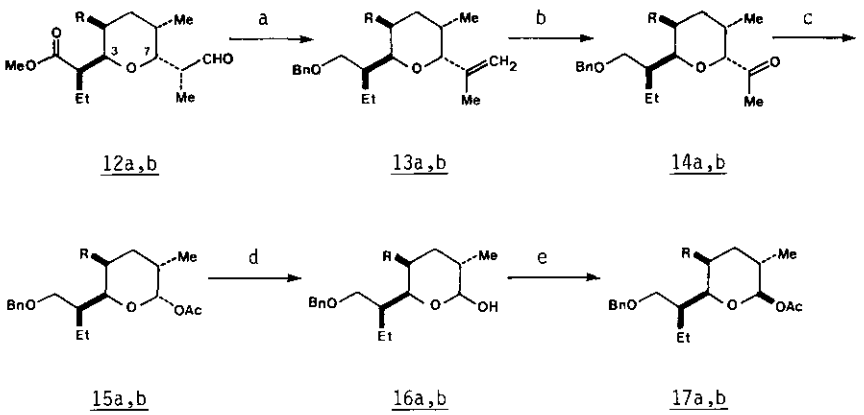
Scheme 5



The tetrahydropyran acetates 15a and 17a required for this study were prepared from the aldehyde 12a, which was readily available by thermally induced retro-aldol reaction of natural narasin (Scheme 6).[8,9] The aldehyde 12a was converted to the olefin 13a in 5 steps in about 65% overall yield. Ozonolysis of 14a, followed by Baeyer-Villiger oxidation, yielded the axial acetate 15a in 90% yield. Hydrolysis of 15a under basic conditions gave a mixture of α- and β-lactols 16a, acetylation of which yielded almost exclusively the equatorial acetate 17a in 85% overall yield. The tetrahydropyran acetates 15b and 17b were also prepared from salinomycin (1b)[10] in a comparable yield by using the same sequence of reactions.

Among several obvious options for the nucleophile, the enol silyl ether 19 seemed most attractive since the C.8 methyl group could directly be introduced. The enol silyl ether 19 was prepared by refluxing propionaldehyde and trimethylsilyl chloride in DMF containing triethylamine.[11] After work-up, distillation furnished a 7:4 mixture of Z- and E-enol silyl ethers 19-Z and 19-E. This mixture was used in all subsequent coupling reactions unless otherwise noted.

Scheme 6



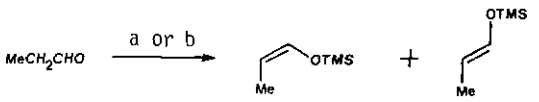
12a,b 13a,b 14a,b

15a,b 16a,b 17a,b

Reagents and conditions

a. 1. $NaBH_4$/MeOH/0°C. 2. o-$O_2NC_6H_4SeCN$/(n-Bu)$_3P$/THF/RT, followed by H_2O_2 treatment/0°C → RT. 3. $LiAlH_4$/Et_2O/0°C. 4. $C_6H_5CH_2Br$/KH/THF-DMF (4/1)/0°C → RT. b. O_3/MeOH/-78°C, followed by $(Me)_2S$ work-up. c. MCPBA/Na_2HPO_4/CH_2Cl_2/RT. d. NaOMe/MeOH/RT. e. Ac_2O/py/RT.

Scheme 7



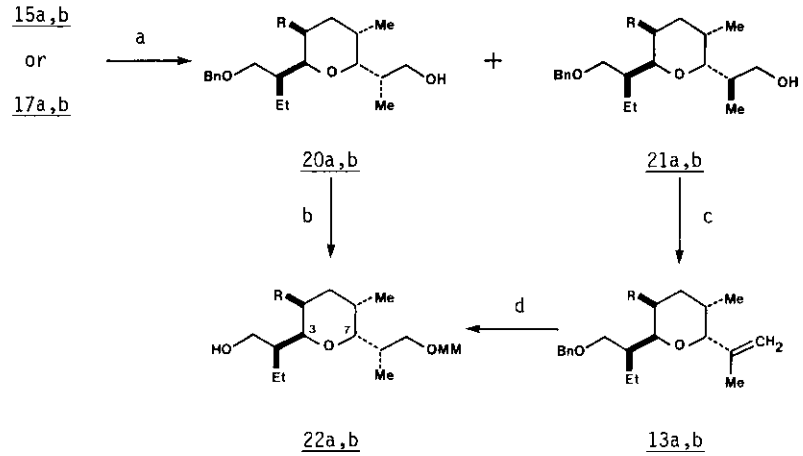
18 19-Z 19-E

Reagents and conditions

a. TMSCl/Et_3N/DMF/reflux (19-Z:19-E = 7:4). b. TMSOTf/Et_3N/Et_2O/0°C→RT (19-Z:19-E = 4:1).

Among a variety of conditions studied, the desired coupling was best achieved by stirring the acetate 15a or 17a with the enol silyl ethers 19-Z,E (4.5 eq) in a 1:1 mixture of methylene chloride and ether in the presence of zinc chloride (excess) at 0°C.[12] The coupling reaction of the acetates 15a and 17a under these conditions, followed by $NaBH_4$ reduction, gave a 3.5:1 mixture of 20a and 21a (77% yield) and a 3.8:1 mixture of 20a and 21a (79% yield), respectively.[13] The structure of major product 20a was established by correlation with the alcohol 22a, one of the intermediates used in the previous synthesis.[2] The structure of minor product 21a was established by correlation with the olefin 13a.

Scheme 8

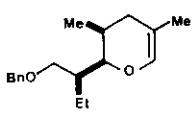


MM=$MeOCH_2$-

Reagents and conditions

a. 19-Z,E (ca. 4.5 eq)/$ZnCl_2$(excess)/CH_2Cl_2/0°C, followed by $NaBH_4$ work-up (MeOH/0°C). b. 1. $BrCH_2OMe/(i\text{-}Pr)_2(Et)N/CH_2Cl_2$/RT. 2. H_2/Pd-C/MeOH/RT. c. $o\text{-}O_2NC_6H_4SeCN/(n\text{-}Bu)_3P$/THF/RT, followed by H_2O_2 treatment/0°C→RT. d. 1. thexylborane/THF/0°C, followed by H_2O_2/OH^- work-up 2. $BrCH_2OMe/(i\text{-}Pr)_2(Et)N/CH_2Cl_2$/RT. 3. H_2/Pd-C/MeOH/RT.

Substantial efforts were made to isolate and identify by-products. Most significant, no equatorial isomer could be isolated. Thus, it is safe to conclude that the carbon-carbon bond formation at the anomeric center took place exclusively[14] as anticipated. In addition to the desired products 20a and 21a, a by-product was isolated in 10 ∿15% yield, the spectroscopic data of which are consistent with the glycal structure 23a. Obviously, 23a was derived from the proposed intermediate 9. In this connection, it is interesting to note that this by-product was formed in much larger extent when one equivalent, instead of 4 ∿5 equivalents, of the enol silyl ethers 19-Z,E was used. In addition to the glycal 23a, a small amount of the lactol 16a was also recovered from the coupling reaction.



23a

The coupling reaction discussed above is not limited only to the narasin series. Parallel results were observed in the salinomycin series; about a 3:1 mixture of the tetrahydropyrans 20b and 21b were obtained from 15b or 17b[13] in comparable chemical yields. Again, no equatorial product was formed.[14] It is interesting to note the fact that the coupling of 15b or 17b with allyltrimethylsilane resulted in approximately a 10:1 ratio of axial to equatorial products. This product ratio is very close to that observed in the carbohydrate examples.[6]

As discussed, the C.8 stereochemistry of the major product 20a,b corresponds to the natural configuration of narasin and salinomycin. Based on the following two observations, it seems safe to conclude that the stereochemical outcome at this center is independent from the configuration of the silyl enol ether 19-Z,E. First, the coupling experiment using a 4:1 mixture[15] instead of a 7:4 mixture of the Z- and E-silyl enol ethers 19 furnished an identical ratio of products. Second, the coupling experiment using only one equivalent of the silyl enol ether also furnished the exact same ratio of products.

The alcohol 22a derived from the major product 20a was an intermediate in the previous narasin synthesis.[2] In addition, an efficient transformation of the minor tetrahydropyran 21a into the same alcohol 22a was successfully developed (Scheme 8). The key step in this transformation was stereoselective thexylborane hydroboration of 13a, yielding almost exclusively the C.8 natural isomer.

Preliminary studies have shown that the lactols 16a can be synthesized in a straightforward manner from an intermediate used in the previous total synthesis of narasin.[2] Thus, the coupling reaction reported in this paper furnishes a new, efficient synthesis of the left half of narasin.

ACKNOWLEDGMENTS

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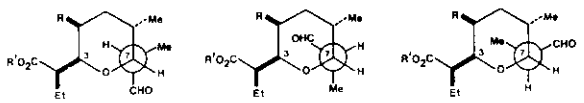
REFERENCES AND FOOTNOTES

1. Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.
2. (a) Y. Kishi, S. Hatakeyama, and M. D. Lewis, Frontiers of Chemistry, 287 (1982). (b) Michael David Lewis, Harvard Dissertation, 1983.
3. In this paper, the compounds belonging to the narasin series are designated as the a series with R=Me, whereas the compounds belonging to the salinomycin as the b series with R=H.

4. This analysis is based on the assumption that 3 exists in a chair conformation.

5. There are 3 gauche conformations A, B and C possible with respect to the C.7-C.8 bond. In general, the conformers like B and C are known to be less preferred over the conformer A.



A B C

6. M. D. Lewis, J. K. Cha, and Y. Kishi, J. Am. Chem. Soc., 104, 4976 (1982).

7. It is interesting also to note that the equilibrium between 9-A and 9-B is probably shifted toward 9-A.

8. We are indebted to Dr. Hamill, Lilly Research Laboratories, Indianapolis, for a sample of natural narasin.

9. This transformation was achieved in 80% overall yield in 3 steps: 1. Ac_2O/py/RT, 2. CH_2N_2/Et_2O/RT, 3. 210°C/0.3 mmHg.

10. We are indebted to Drs. Fujita and Esumi, Kaken Chemical Co., Tokyo, for a sample of salinomycin.

11. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. Z. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).

12. During these studies, C-glycosidations using enol silyl ethers were reported. See (a) S. Murata and R. Noyori, Tetrahedron Lett., 23, 2601 (1982). (b) R. R. Schmidt and M. Hoffman, Angew. Chem. Int. Ed. Engl., 22, 406 (1983). (c) R. M. Williams and A. O. Stewart, Tetrahedron Lett., 24, 2715 (1983).

13. Separation of 20a,b and 21a,b was easily achieved by silica gel column or preparative thin layer chromatography.

14. Formation of a small amount (<2% yield) of equatorial products could not be ruled out from these experiments.

15. This mixture was prepared by adding trimethylsilyl triflate to a solution of propionaldehyde in ether and triethylamine at 0°C: H. Emde, A. Gotz, K. Hofmann, and G. Simchen, Liebigs Ann. Chem., 1643 (1981).

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