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Asymmetric Synthesis of the AB Ring System of Lactonamycin

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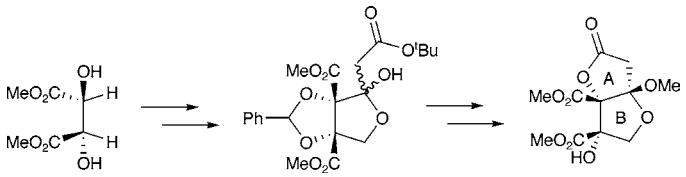
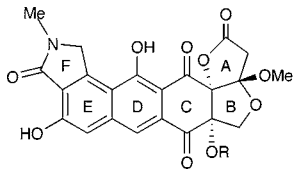
ABSTRACT



An enantiospecific synthesis of the AB fragment of lactonamycin (5) is achieved in eight steps from dimethyl D-tartrate. Ester enolate chemistry features prominently in the sequence.

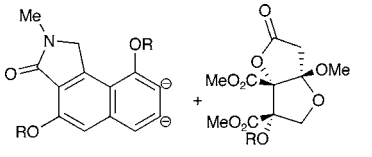
The antibiotic lactonamycin (**1a**)[1] and its recently reported congener lactonamycin Z (**1b**)[2] have a hexacyclic core unlike that of any other natural product. Lactonamycin also exhibits potent (sub μg/mL minimum inhibitory concentration, MIC) activity against a wide range of bacterial strains, including ones that withstand current antibiotics. The pressing need for new antibiotics effective against resistant bacterial infections and the unique structure of the lactonamycin core have stimulated considerable interest in the synthesis of these molecules.



1a, R = α-L-rhodinose
1b, R = α-L-2,6-dideoxyribose
2, R = H

To date, three laboratories have reported on their efforts toward the synthesis of lactonamycin. Danishefsky and Cox recorded some exploratory studies[3] on the construction of the ABC[4] ring system; more recently, Danishefsky, Cox, and Siu have described a synthesis of (±)-lactonamycinone (**2**),[5] the aglycon of **1**. Deville and Behar[6] and our laboratory[7] have published routes for the construction of the CDEF ring system.

One possible enantiospecific approach to **1** is suggested in eq 1, involving the union of two (sequentially generated) anionic centers in **3** with enantiomerically pure diester **4**. We now describe an enantiospecific synthesis of **4**'s equivalent: **5**.



3 **4**, R = protecting group or sugar
5, R = H

(1)

Retrosynthetic analysis (eq 2) suggested that **5** might be derived from dimethyl tartrate. Compound **5** maps most

(1) See: Matsumoto, N.; Tsuchida, T.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Naganawa, H.; Iinuma, H.; Sawa, T.; Takeuchi, T.; Shiro, M. *J. Antibiot.* **1999**, *52*, 276−280 and references therein.

(2) Höltzel, A.; Dieter, A.; Schmid, D. G.; Brown, R.; Goodfellow, M.; Beil, W.; Jung, G.; Fiedler, H.-P. *J. Antibiot.* **2003**, *56*, 1058−1061.

(3) (a) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493−3496. (b) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899−2902.

(4) The rings in **1** and **2** have been assigned letters in accord with ref 1. Others (refs 3, 5, and 6) have used a different lettering scheme.

(5) (a) Cox, C. D.; Siu, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5625−5629. (b) Siu, T.; Cox, C. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5629−5634.

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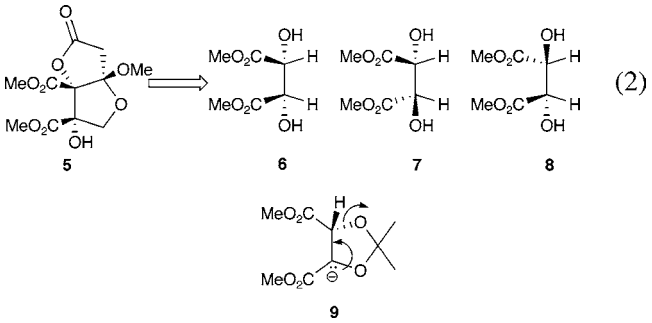
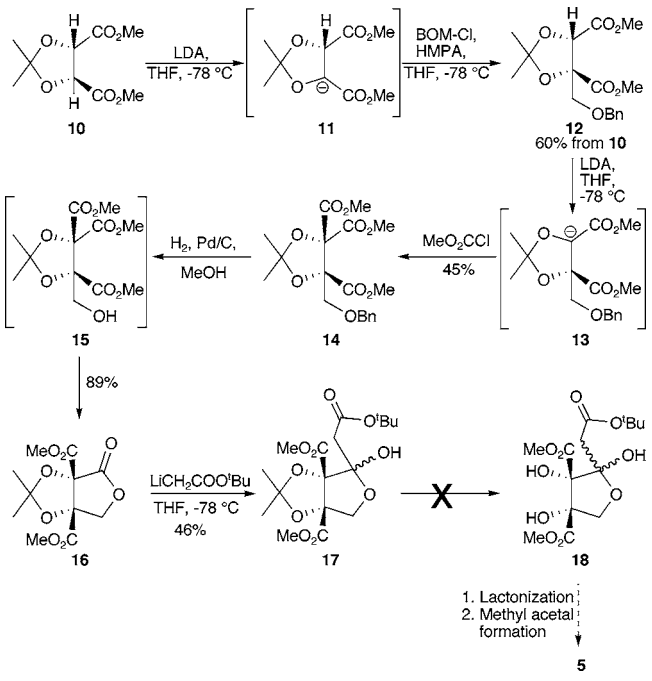
directly to meso tartrate (**6**), but for an enantioselective synthesis, optically active L- (**7**) or D-tartrate (**8**) would be preferred, with one of the stereocenters being "inverted" during the elaboration of **5**. It was anticipated that **7** or **8** might be advanced to **5** using enolate chemistry. Prior work by Seebach,[8] Evans,[9] and Leighton[9a,10] had established that cyclic acetals of tartrate such as acetonides can be converted to their enolates (see **9**) and usefully elaborated, with tendencies toward β-elimination (arrows in **9**) being diminished by the poor orbital alignment imposed by the cyclic acetal.

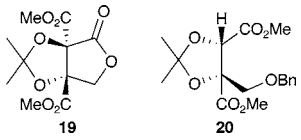


(2)

Accordingly (Scheme 1), known[11] acetonide **10**, readily derived in two steps from D-tartaric acid, was converted to its enolate (**11**), which was alkylated with benzyloxymethyl chloride (BOM-Cl) to give **12** as the only stereoisomer detected. The stereochemistry of **12** was assigned on the basis of NOESY[12] measurements. Deprotonation of the remaining enolizable center gave enolate **13**, which was trapped with methyl chloroformate to afford triester **14**. Hydrogenolysis of **14** generated **15** which cyclized to **16** spontaneously under the reaction conditions. Either of the two geminal carbomethoxys in **15** could have cyclized, giving either cis-fused lactone **16** or its trans-fused stereoisomer **19**. The desired cis-fused 5,5 ring system of **16** is strongly favored thermodynamically, and **16** is, according to X-ray analysis,[12] the stereoisomer produced.[13,14]

Scheme 1





Reaction[15] of lactone **16** with the lithium enolate of *tert*-butyl acetate[16] provided an inseparable mixture of one diastereomer of **17** and a then-unidentified[17] second compound. Compound **17** contains all of the carbon atoms of **5**, and an optimist could argue that conversion of **17** to **5** might be achieved in a single operation (treatment with acidic methanol). But with the end in sight, the synthesis of **5** floundered, as **17** could not be advanced productively, despite extensive efforts. The principal problem was the inability to fruitfully cleave the acetonide under a wide range of reaction conditions.

Consequently, it was decided to examine different protecting groups, with particular attention paid to those potentially removable under oxidative or hydrogenolytic conditions. Dimethyl D-tartrate was thus protected as the acetal of the series of aldehydes and ketones listed in Figure 1.[18] All of

(6) Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403−1405.
(7) Kelly, T. R.; Xu, D.; Martínez, G.; Wang, H. *Org. Lett.* **2002**, *4*, 1527−1529.

(8) Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030−1031.
(9) (a) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111−12112. (b) Evans, D. A.; Trotter, B. W.; Barrow, J. C. *Tetrahedron* **1997**, *53*, 8779−8794.
(10) See also Leighton, J. L. Ph.D. Thesis, Harvard University, Cambridge, MA, 1994.
(11) (a) Kim, B. M.; Bae, S. J.; So, M. S.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. *Org. Lett.* **2001**, *3*, 2349−2351. (b) Mash, E. A.; Nelson, K. A.; Van Deusen, S.; Hemperly, S. B. *Org. Synth.* **1990**, *68*, 92−103.
(12) See the Supporting Information.
(13) It is perhaps noteworthy that although both stereocenters in **10** are rendered liable to stereochemical randomization, since enolate generation was done successively rather than simultaneously, absolute stereochemical information was not lost.[14] Indeed, if the alkylation of **11** had proceeded with inversion instead of retention of configuration at the enolized carbon, to give **20** rather than **12**, then the quick fix would simply have been to replace **10** with its L-tartrate-derived enantiomer. Only (not observed) if reaction of **11** with BOM-Cl gave something approximating a 1:1 mixture of **12** and **20** would stereochemical control of an asymmetric synthesis (but not of a racemic synthesis) have been at risk.
(14) For a review on the self-regeneration of stereocenters, see: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748.
(15) It was assumed that attack would occur at the lactone carbonyl because lactones are known to be much more reactive than esters toward nucleophiles: See Huisgen, R.; Ott, H. *Tetrahedron* **1959**, *6*, 253−267.
(16) Only this enolate provided the expected product; the use of ethyl, benzyl, or isopropyl acetate resulted in partial decomposition of **16**.
(17) In retrospect, we believe the second compound is an acetonide analogue of **35**/**36**.
(18) See the Supporting Information. We were also able to synthesize the cyclic silyl derivative[19] prepared from di-*tert*-butylsilyl bistriflate, but it could not be converted to the BOM derivative analogous to **31**.

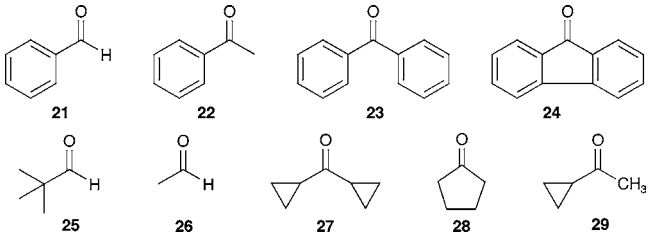
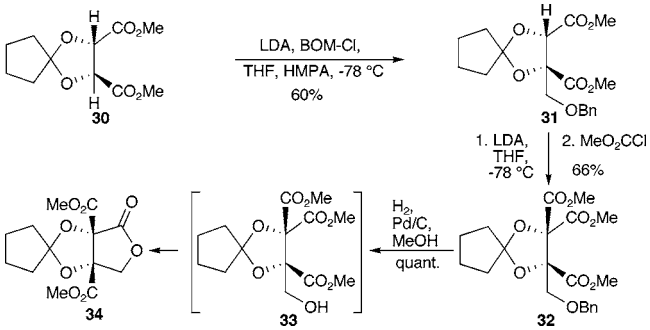


Figure 1. Aldehydes and ketones examined for protecting tartrate diol unit as an acetal.[18]

these acetals were prepared, but unfortunately, only the cyclopentylidene acetal successfully underwent the alkylation with BOM-Cl. In the other cases, decomposition of the starting acetal was observed, due presumably to β-elimination.

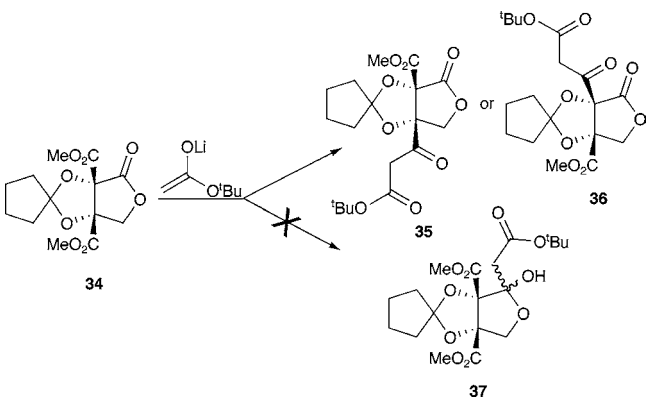
Because cyclopentylidene acetals have been found more labile than acetonides,[20] it was decided to repeat the earlier synthesis (Scheme 1) using a cyclopentylidene acetal in place of the acetonide (Scheme 2). In fact, the synthesis of the

Scheme 2



antipode of **31** had already been reported by Crich and Hao.[21] Elaboration of **31** to lactone **34** proved straightforward (Scheme 2). Reaction of **34** with the anion of *tert*-buyl acetate, however, went awry[15] (Scheme 3). In contrast to the

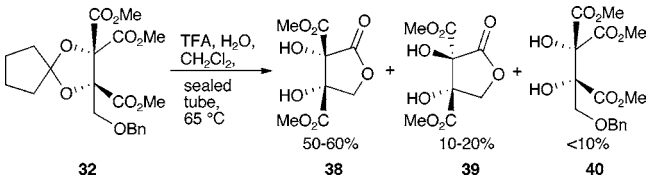
Scheme 3



outcome found with acetonide **16**, reaction occurred at one of the ester carbonyls to give **35** or **36**, rather than at the lactone carbonyl to give the desired **37**.

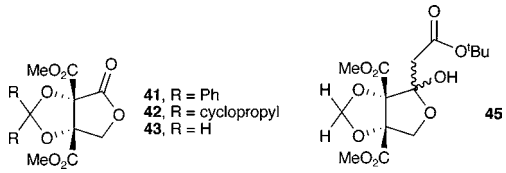
Since the only difference between **34** and **16** is the protecting group, we sought to evaluate the effect of other protecting groups. The cyclopentylidene unit in **34** could not be cleaved. However, attempted hydrolysis of the acetal in precursor **32** with CF_3COOH not only removed the cyclopentylidene but also (Scheme 4), providentially, induced

Scheme 4



benzyl ether cleavage and cyclization to give **38** along with lesser amounts of **39** and **40**. That **38** was, in fact, the desired cis diol stereoisomer was established by X-ray analysis.[12]

Efforts to reprotect **38** with symmetric, potentially labile acetal protecting groups as in **41** and **42**[10] failed. The methylenedioxy derivative **43** could be prepared, and it reacted with $LiCH_2COO^tBu$ in the presence of $TiCl_4$ (see below) to give **45**, but the methylenedioxy could not be cleaved, even oxidatively.[22,23]



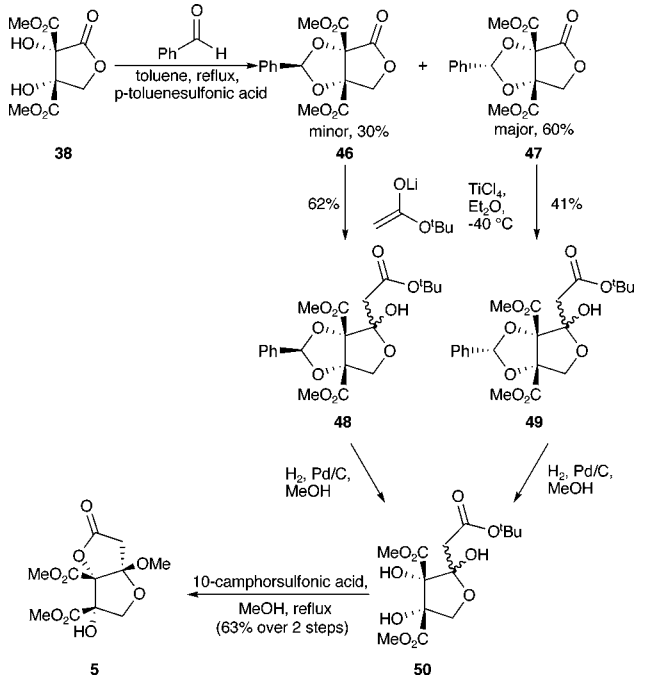
Two parallel efforts were then launched. One was to examine the effect of addition of Lewis acids on the outcome of the reaction in Scheme 3. A variety of Lewis acids was screened, including[25] $MgCl_2$, $ZnCl_2$, $BF_3{\cdot}E_2O$, and $TiCl_4$. $TiCl_4$ was found to be especially effective in redirecting the course of the reaction in Scheme 3; in particular, inclusion of 1 equiv of $TiCl_4$ produced **37** as the major product. But the cyclopentylidene in **37** was inert to hydrolysis and could not be removed.

Simultaneously, additional evaluation of protecting groups was undertaken.

Escape from the abyss was accomplished by converting **38** to its benzylidene derivative(s) **46** and **47** which were produced (Scheme 5) as a separable 1:2 mixture of diaste-

(19) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999−5002.
(20) van Heeswijk, W. A. R.; Goedhart, J. B.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1977**, *58*, 337−344.
(21) Crich, D.; Hao, X. *J. Org. Chem.* **1999**, *64*, 4016−4024.
(22) (a) Pattenden, G.; Smith, G. F. *Tetrahedron Lett.* **1990**, *31*, 6557−6560. (b) Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465−2467. (c) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651−3664.

Scheme 5

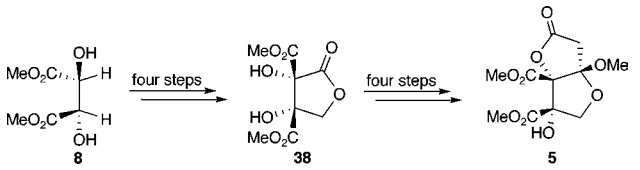


reoisomers.[26] Both diastereomers reacted with $LiCH_2COO^tBu$ in the presence of $TiCl_4$ to give desired adducts **48** and **49**. Hydrogenolysis of both of the latter then cleaved the protecting group, giving **50**, in each case as a mixture of hemiacetal diastereomers.

Having been conditioned by all that went before to expect serious difficulty at every step, the conclusion of the synthesis was refreshingly straightforward. Treatment of crude **50** with methanolic camphorsulfonic acid initiated a cascade of events involving methyl acetal formation, anomerization, and lactone closure to afford the target **5** in 63% yield from **48**/**49**. The stereochemistry of the methoxy group in **5** was dictated by a combination of starting D-tartrate stereochemistry, equilibrating reaction conditions and the thermodynamic imperative favoring cis- versus trans-fused 5,5 ring systems. Reassuringly, X-ray crystallography confirmed both the connectivity and relative stereochemistry assigned to **5**.[12]

In conclusion, as summarized in Scheme 6, an enantiospecific synthesis of **5** has been achieved in eight steps from commercially available dimethyl D-tartrate. Elaboration of **5** to lactonamycin is underway.

Scheme 6



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Supporting Information Available: Experimental procedures and characterization data for selected compounds, including NOE difference and NOESY spectra. X-ray structure data for **5**, **16**, **38**, and **39** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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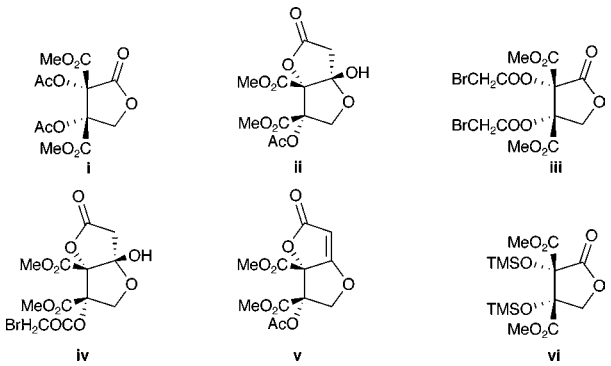
(23) Diol **38** could be converted to diacetate **i**, but despite seemingly compelling precedent,[24] **i** could not be induced to undergo intramolecular cyclization to **ii**. Bisbromoacetate **iii** could also be prepared, but attempts to cyclize it to **iv** or **v** using Favorski- or Wittig-based chemistry were also unavailing. The bis TMS ether **vi** could be prepared but in the absence of $TiCl_4$ it gave a **35**/**36** type adduct with $LiCH_2COO^tBu$, while in the presence of $TiCl_4$ recovery of **vi** was observed.



(24) Kraus, G. A.; Wang, X *Synlett* **1999**, 1395−1396.

(25) For examples of Lewis acid additives modulating the reactivity of lithium enolates see House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324.

(26) Stereochemistry assigned using NOE difference experiments.[12]