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Stereoselective Synthesis of the Western Hemisphere of Salinomycin

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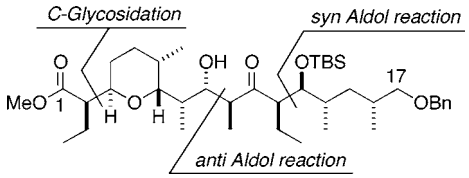
ABSTRACT



A convergent and module-based strategy for the asymmetric synthesis of the western hemisphere (C1–C17 fragment) of salinomycin has been devised. This new synthetic approach relies on highly stereoselective C-glycosidation and aldol processes.

Salinomycin (**1**, Figure 1) is a polyether ionophore antibiotic first isolated from a culture broth of *Streptomyces albus* in

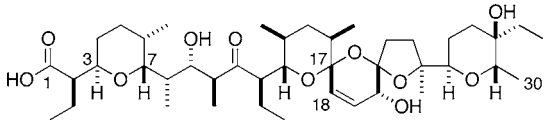


Figure 1. Salynomicin (**1**).

1973 and is widely recognized by its remarkable antibacterial and anticoccidial properties.[1,2] Structurally, its molecular architecture is dominated by the presence of a plethora of chiral centers embedded in a polyoxygenated backbone, which encompass two substituted tetrahydropyrans and a complex tricyclic bis-spiroacetal system. Then, it is not surprising that the appealing biological properties combined with the synthetic challenge raised by such intricate and densely functionalized structure have stimulated much synthetic efforts, which have culminated in three total syntheses[3−5] and new approaches to the spiroacetal core.[6]

In our case, we were particularly attracted by the tetrahydropyran ring flanked by an α-alkyl acetic acid and a polyketide chain at the C3 and C7 positions, respectively (Scheme 1), a structural arrangement that salinomycin shares with other prominent polyether ionophore antibiotics such as narasin, zincophorin, and X-206.[2] Recognition of this structural motif suggested to us the opportunity of devising a common approach to the total synthesis of these molecules. Supporting this new approach, we document herein a highly stereoselective construction of the C1−C17 fragment of salinomycin based on C-glycosidation[7] and substrate-controlled aldol[8] processes developed in our group.

(1) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, *49*, 4955−4958.

(2) For recent reviews on polyether ionophore antibiotics, see: (a) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165−181. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473.

(3) First total synthesis of salinomycin disclosed by Y. Kishi in 1982 has been solely published as a lecture. For further comments, see ref 2b.

(4) (a) Horita, K.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1698−1704. (b) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1705−1716. (c) Horita, K.; Oikawa, Y.; Nagato, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1717−1725. (d) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1726−1730.

(5) Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 9−39.

(6) For a review, see: Brimble, M. A.; Farès, F. A. *Tetrahedron* **1999**, *55*, 7661−7706.

(7) Larrosa, I.; Romea, P.; Urpí, F.; Balsells, D.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651−4654.

(8) (a) Figueras, S.; Martín, R.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*, 1637−1640. (b) Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2599−2602. (c) Solsona, J. G.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519−522. (d) Solsona, J. G.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2004**, *45*, 5379−5382.

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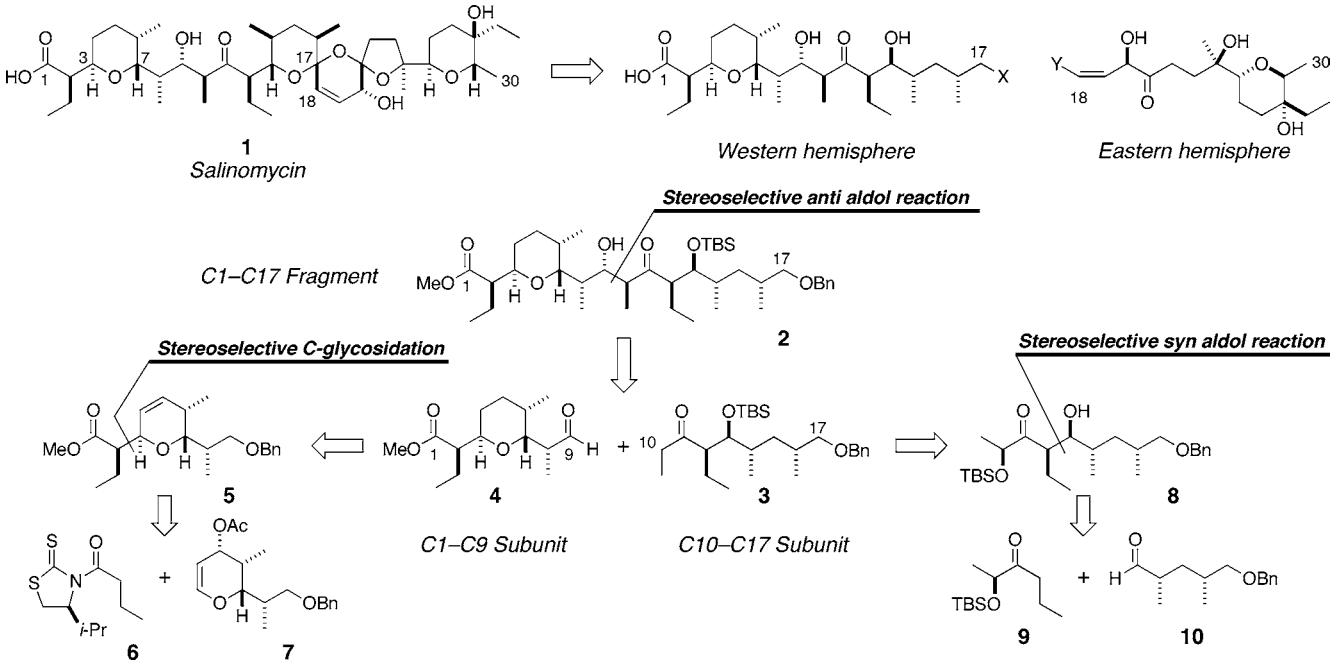
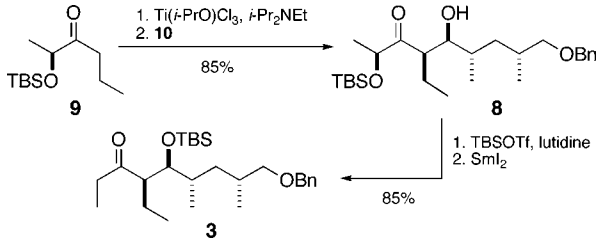
Scheme 1. Retrosynthetic Analysis of Salinomycin



As outlined in Scheme 1, our retrosynthetic analysis relies on the strategic disconnection of the C17−C18 bond. Thus, salinomycin is split in two halves of similar size and structural complexity that we have named *hemispheres*. Further elaboration of the *western* hemisphere reveals the protected C1−C17 fragment **2** shown in Scheme 1 as our actual target. Following this analysis, we anticipated that the successful construction of **2** would mainly depend on three crucial steps: (i) a double asymmetric *anti* aldol reaction of ketone **3** and aldehyde **4**; (ii) a Lewis acid mediated C-glycosidation involving titanium enolate from (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**6**) and glycal **7**; and (iii) a double asymmetric *syn* aldol reaction arising from α-hydroxy ketone **9** and aldehyde **10**. In summary, our synthetic approach is rooted in a highly convergent and module-based strategy that depends on the stereoselective coupling of subunits represented in Scheme 1.

Keeping in mind these ideas, we first proceeded to the synthesis of the C10−C17 subunit **3**. Taking advantage of the highly stereoselective titanium-mediated aldol reactions based on lactate-derived ketones developed in our group,[8] we envisaged that it could arise from a *matched* double asymmetric aldol reaction.[9] Particularly, the synthesis of ketone **3** began with a titanium-mediated aldol reaction of the readily available α-*tert*-butyldimethylsilyloxy ketone **9**[10] and chiral aldehyde **10**[11] (Scheme 2). Enolization of **9** with Ti(*i*-PrO)Cl_3/*i*-Pr_2NEt followed by the addition of a solution of **10** at −78 °C provided the corresponding *syn*/*anti* Felkin aldol adduct **8** as a single diastereomer (85%, dr > 97:3). Finally, protection of the C13 alcohol and regioselective removal of the C10 OTBS group using SmI_2 [12] afforded the required ketone **3** in 85% yield over the two-step procedure from **8**.

Scheme 2. Synthesis of the C10−C17 Subunit **3**



Having prepared the C10−C17 subunit, our attention was focused on the preparation of the tetrahydropyran moiety. Studies on C-glycosidation processes involving titanium enolates derived from *N*-acyl-1,3-thiazolidine-2-thiones have established that the stereochemical outcome of such cross-coupling reactions mainly depends on the C6 group of the glycal and the configuration of the chiral auxiliary.[7] In our case, ester **5** might arise from *N*-butanoyl derivative **6** and glycal **7** shown in Scheme 1. Then, simultaneous hydrogenation of the alkene and removal of the benzyl protecting group followed by oxidation of the resulting alcohol should lead to the C1−C9 subunit **4**.

(9) For double asymmetric aldol reactions involving lactate-derived ketones, see: Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. *Synlett* **2004**, 2127−2130.

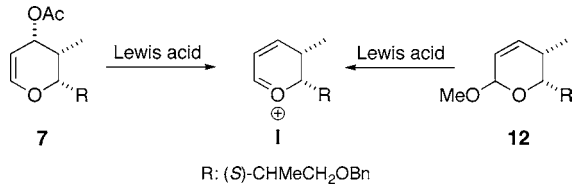
(10) Ferreró, M.; Galobardes, M.; Martín, R.; Montes, T.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Synthesis* **2000**, 1608−1614.

(11) Chiral aldehyde **10** was prepared by Swern oxidation of the parental alcohol, which in turn was obtained following reported procedures. See: Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003**, *5*, 1617−1620.

(12) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652.

In accordance with this analysis, we applied our efforts to preparing glycal **7**. Unfortunately, no stereoselective methodology afforded it in synthetically useful amounts. This failure jeopardized the whole approach, and we were required to modify our plans. Close inspection of the crucial C-glycosidation step suggested that other options could be considered. Indeed, although the mechanistic details of the above-mentioned *C*-glycosidation procedure are still under scrutiny, it is likely that the reaction proceeds through the oxocarbenium **I** shown in Scheme 3 via an S_N1-like process.

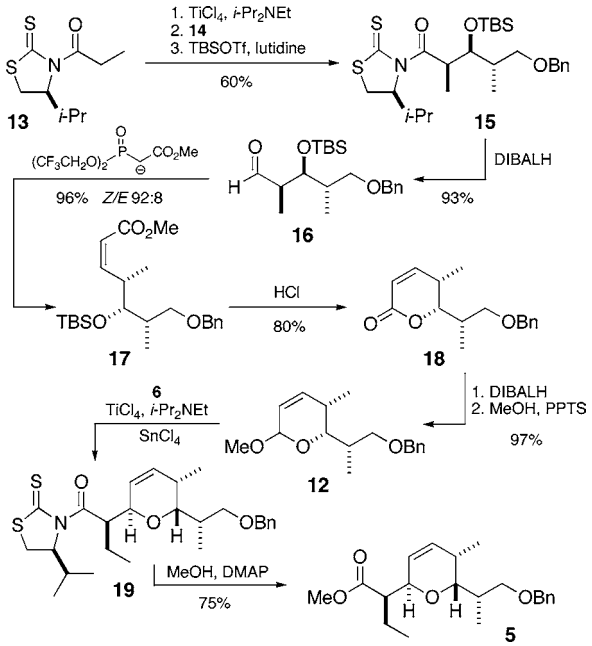
Scheme 3



Therefore, glycal **7** might be replaced by any other species able to provide the putative cationic intermediate **I** by means of Lewis acid activation, such as pseudoglycal **12** represented in Scheme 3.

Then, all of the stereocenters present in the required oxocarbenium **I** were envisaged to arise from a stereoselective aldol reaction. According to this approach, titanium-mediated aldol[13] reaction of (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**13**) and (*S*)-3-benzyloxy-2-methylpropanal (**14**)[14] followed by treatment of the resulting diastereomeric mixture with TBSOTf/lutidine provided enantiomerically pure protected aldol **15** in 60% yield over two steps after a simple chromatographic purification (Scheme 4). Next, clean removal of the chiral auxiliary with DIBALH produced aldehyde **16** in a single step and excellent yield.[15] Submission of **16** to Still−Gennari olefination conditions[16] afforded α,β-unsaturated ester **17** (96% yield, *Z*/*E* ratio 92:8), which was easily converted into lactone **18**. Finally, a two-step sequence based on a DIBALH reduction of **18** and *O*-methyl glycosidation of the resulting lactol afforded the desired pseudoglycal **12** as a mixture of diastereomers (dr 90:10) in 97% yield. The stage was now set for the critical C-glycosidation step. Gratifyingly, experimental conditions previously optimized for glycals[7] could be successfully applied to (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione (**6**) shown in Scheme 1 and pseudoglycal **12** in such a way that adduct **19** was isolated as a single diastereomer (dr > 97:3 by ^{1}H NMR). At this point, configuration of new stereocenters C2−C3 was secured through extensive 1D and 2D NMR analysis.

Scheme 4. Synthesis of the C1−C9 Ester **5**

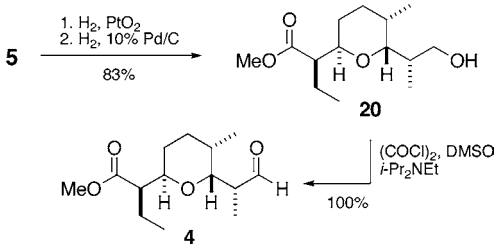


Furthermore, no chromatographic purification of the reaction mixture was required and methyl ester **5** was smoothly obtained in 75% overall yield from **12** by removal of the chiral auxiliary with methanol in the presence of catalytic DMAP at room temperature, as shown in Scheme 4.

With methyl ester **5** in hand, it was envisaged that simultaneous hydrogenation of the C4−C5 double bond and cleavage of the C9 benzyl ether followed by oxidation of the resulting alcohol would afford the C1−C9 subunit **4** shown in Scheme 1. However, submission of **5** to the usual reductive conditions employing 10% Pd/C as catalyst provided the expected hydroxy ester **20** contaminated by *epi*-C3 diastereomer **21**.[17]

After careful optimization, it was established that formation of the undesired diastereomer **21** could be avoided applying a two-step sequence: C═C double bond hydrogenation in the presence of PtO_2, followed by hydrogenolysis of the benzyl protecting group with 10% Pd/C as catalyst (Scheme 5). At this point, the stereochemical array of **20** was nicely confirmed through comparison with the spectroscopic data previously reported.[4d] Eventually, Swern oxidation of alcohol **20** completed the synthesis of the C1−C9 subunit **4**.

Scheme 5. Synthesis of the C1−C9 Subunit **4**: Final Steps



(13) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

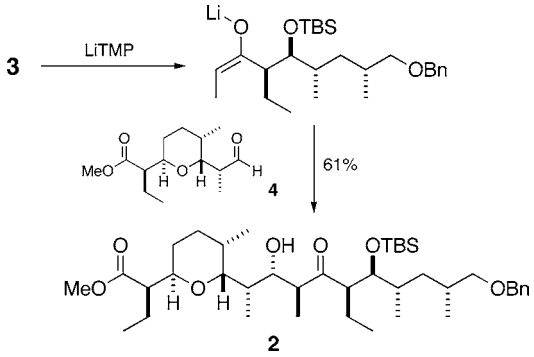
(14) Roush, W. R.; Palkowitz, A. D.; Palmer, M. J. *J. Org. Chem.* **1987**, *52*, 316−318.

(15) Spectroscopic data of **16** match those of *ent*-**16** previously reported. See Supporting Information.

With key subunits **3** and **4** in hand, we faced their crucial coupling to obtain the required C1−C17 fragment **2**. Since initial studies highlighted how heating of salinomycin derivatives triggers a clean retroaldol reaction affecting the C9−C10 bond, the synthetic approaches reported so far rely on the construction of such strategic bond through a stereoselective aldol reaction.[2−5] In our case, the scenario was designed for a boron-mediated double asymmetric aldol reaction.[18] However, enolization of **3** with Chx_2BCl/Et_3N followed by addition of aldehyde **4** gave low and nonreproducible yields. Fortunately, the more reactive (*E*) lithium enolate counterpart[19] provided the double asymmetric *anti* aldol reaction stereoselectively (dr 90:10), and a simple purification by flash chromatography permitted the isolation of enantiomerically pure C1−C17 fragment **2** in 61% yield, as outlined in Scheme 6.

In summary, we have disclosed a concise and efficient route to the asymmetric construction of the western hemisphere of salinomycin, which is based on highly stereoselective C-glycosidation and substrate-controlled aldol processes. Our synthetic approach is rooted on a convergent and module-based strategy that could be applied to the synthesis of other prominent polyether ionophore antibiotics.

Scheme 6. C1−C17 Fragment **2**: Final Coupling



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Supporting Information Available: Experimental procedures and physical and spectroscopic data, including copies of ^1H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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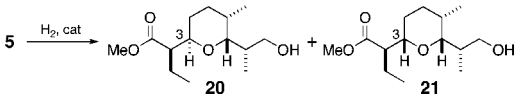
(16) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(17) The mechanistic details of such isomerization are unclear, but migration of the C=C bond promoted by the catalyst followed by nonstereoselective hydrogenation is presumably the cause of this undesired secondary reaction.



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(19) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957−1960.