Pergamon

*Tetrahedron Letters*, Vol. 35, No. 41, pp. 7609-7612, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01591-0

# 1,2-ASYMMETRIC INDUCTION IN THE [2,3]-THIA-WITTIG REARRANGEMENT APPLIED TO A SYNTHESIS OF THE $C_{17}$-$C_{22}$ SUBUNIT OF IONOMYCIN

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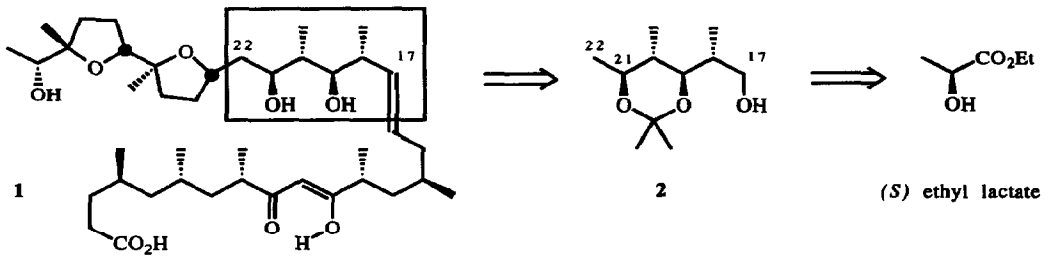
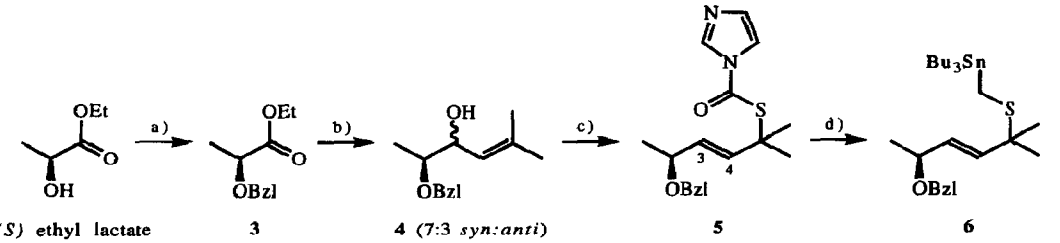
***Abstract***: The title compound **2** was synthesized from (*S*) ethyl lactate in 10 steps. They include a highly diastereoselective [2,3] thia-Wittig rearrangement (**9**→**10**), a chemoselective desulfurization in the presence of a C=C bond (**8**→**12**), and the generation of allylic alcohol **14** from LDA and epoxide **13** obtained under Mihelich's conditions.

Ionomycin (**1**) [1] is a naturally occurring ionophore whose structural complexity and biological activity make it an attractive target molecule for synthetic organic chemists. Partial structures of ionomycin have been synthesized in the Wuts [2], Schreiber [3], Weiler [4], Taschner [5], and Lautens [6] laboratories whereas successful total syntheses are due to Hanessian [7] and Evans [8] and their respective associates. Here we report a stereoselective synthesis [9] of the $C_{17}$-$C_{22}$-subunit **2** of the ionophore. It requires 10 steps from *(S)* ethyl lactate, exploits a similar degree of stereocontrol through 1,2-asymmetric induction in a [2,3]-thia-Wittig rearrangement as described earlier for analogous [2,3]-oxa-Wittig rearrangements [10], and exhibits a total yield of 12%.



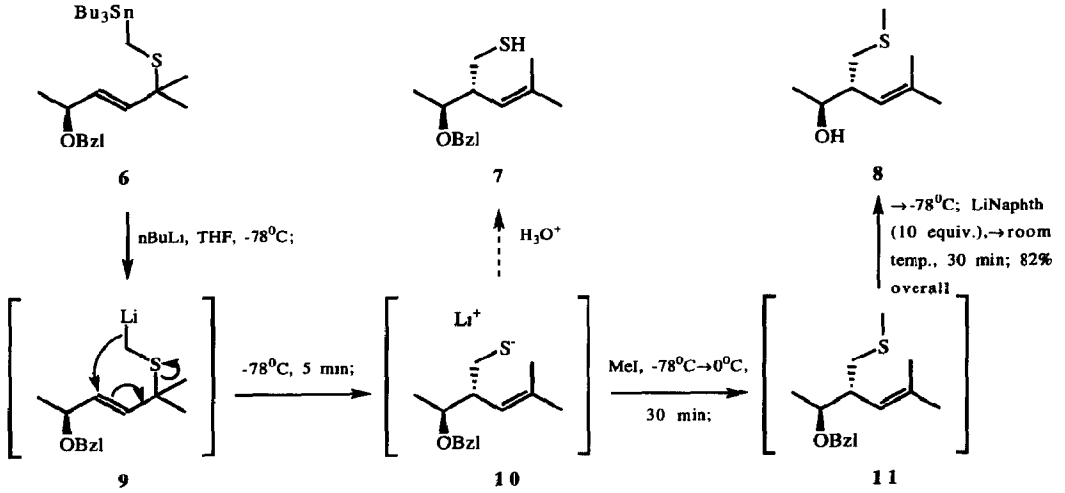

*Scheme 1.*

In our work, the stereocenter C-21 of **2** was taken from (*S*) ethyl lactate (Scheme 1) while the other stereocenters were newly formed. (*S*) ethyl lactate was protected as benzyl ether **3** [11] (Scheme 2) which was converted - in a one-pot procedure [12] - through reduction and alkenyllithium addition into the diaste-




*Scheme 2: a) BzlBr (1.5 equiv.), $Ag_2O$ (1.1 equiv.), $Et_2O$, reflux, 3h; 76%.- b) (i) DIBAH (1.0 equiv.), hexane, -78°C, 1 h; (ii) isobutenyllithium {from 1-bromoisobutene (2 equiv.) and tert-BuLi (5 equiv.) in $Et_2O$ [-78°C, 1h → (2h) 0°C, 1h]}, - 78°C, 15 min → (30 min) room temp., 1.5h; 69%.- c) Thiocarbonyl diimidazolide (3 equiv.), acetonitrile, room temp., 2h; 75%.- d) NaOEt (1.2 equiv.), EtOH, room temp., 15 min; $Bu_3SnCH_2I$ (1.2 equiv.), room temp., 10 min; 88%.*

reomeric alcohols **4**, the major constituent being the *syn* isomer according to the criterion of Landmann and Hoffmann [13]. The alcohols **4** were acylated with $S{=}C(imidazole)_2$ whereupon - still at room temperature - a [3,3] rearrangement occurred delivering the *trans*-configured ($J_{3,4}$ = 15.6 Hz) (allylthio)carbonyl imidazolide **5** [14]. From the latter, a thiolate was obtained through alcoholysis (NaOEt/EtOH). This thiolate was etherified *in situ* by the Seyferth reagent $Bu_3SnCH_2I$ [15] to provide the stannylated sulfide **6**.

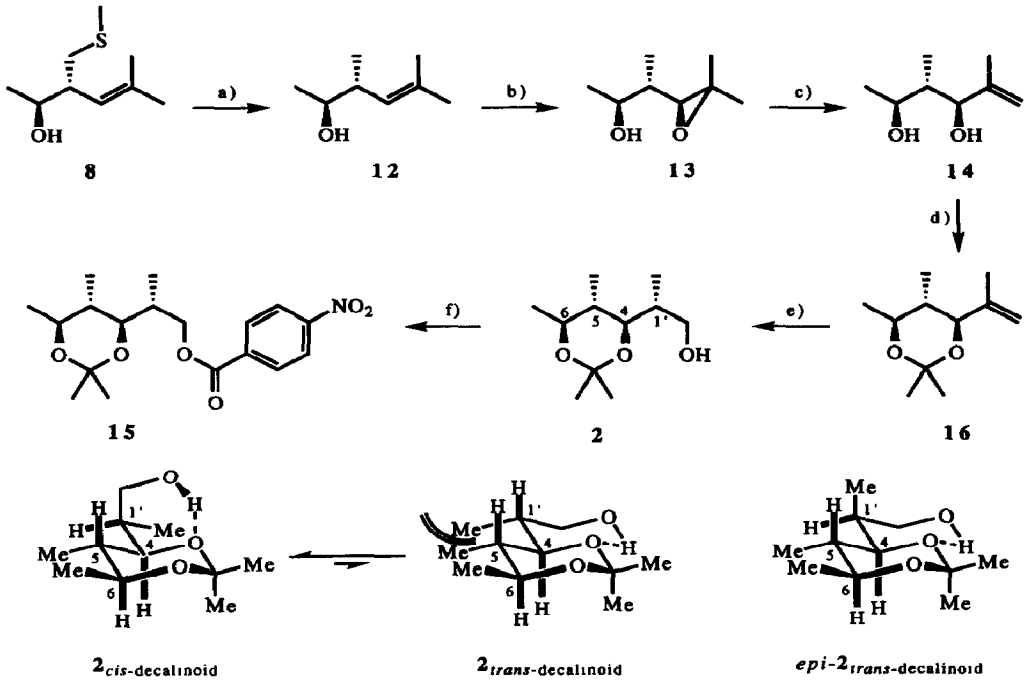



*Scheme 3.*

An *n*BuLi induced Sn/Li exchange in **6** gave the lithiated sulfide **9** which underwent a rapid [2,3]-thia-Wittig rearrangement at -78°C in THF and afforded homoallyl thiolate **10** stereoselectively (Scheme 3). This kind of stereocontrol through asymmetric induction by an allylic oxygen-bearing stereocenter was expected in analogy to previous investigations of [2,3]-thia- [16] and [2,3]-oxa-Wittig rearrangements [10]. When quenched with water the rearranged lithium thiolate **10** could be isolated as thiol **7**. More advantageously, however, and still in the same pot we transformed **10** through methylation (→**11**) and debenzylation with lithium naphthalenide [17] directly into the methylthio alcohol **8**.

Subsequently, alcohol **8** was desulfurized by excess Raney Ni (→**12**, Scheme 4). The concomitant preservation of the C=C bond was ensured by diluting the usual solvent ethanol [18] with cyclohexene; we reasoned that the C=C bond of the latter would be attacked in preference to that of **12** because of its greater abundance. Hydroxyl directed epoxidation of the homoallylic alcohol **12** led to a single epoxide **13** as expected [19]. **13** was ring-opened with LDA providing the 1,3-diol **14** through a regioselective $\beta$-elimination

at the less hindered site. **14** was protected as acetonide **16**. Finally, hydroboration of the *gem*-disubstituted C=C bond of **16** with 9-BBN followed by $HOO^-Na^+$ oxidation gave an isomerically pure alcohol [20].




*Scheme 4: a) W2 Raney Ni, EtOH/cyclohexene 1:1, room temp., 2-28h (GLC monitoring); 75%.- b) tert-BuOOH (1.5 equiv.), $VO(acac)_2$ (cat.), $CH_2Cl_2$, 0°C → room temp., 1h; 78%.- c) LDA (3 equiv.), THF, -78°C, 2h, room temp., 30 min; 88%.- d) $Me_2C(OMe)_2$/acetone 1:1, p-TsOH (cat.), molecular sieves (4Å); yield not determined.- e) 9-BBN, THF, -78°C (1h) → 0°C (2d), then EtOH, NaOH, $H_2O_2$, room temp., 8h; 83% from 16.- f) p-$O_2N$-$C_6H_4COCl$, $NEt_3$, $CH_2Cl_2$, reflux, 2d; 64%.*

By $^1$H-NMR spectroscopy we could not distinguish whether this alcohol was compound **2** or the 1'-epimer *epi*-**2**. Either isomer should possess a chair conformation dioxane ring [21] and in addition a six-membered chair-conformation *hydrogen-bonded* ring. In epimer *epi*-**2** the two chairs should be annulated in the more stable *trans*-decalin fashion ($epi\text{-}2_{trans\text{-decalinoid}}$). However, compound **2** should prefer stereostructure $2_{cis\text{-decalinoid}}$ since $2_{trans\text{-decalinoid}}$ should be destabilized by *syn*-pentane strain [22] between the 1'-methyl and 4-methyl groups. The experimental $J_{vic}$ values $J_{1',4}$ = 2.0 Hz, $J_{4,5}$ = 10.5 Hz, and $J_{5,6}$ = 9.8 Hz of our alcohol agree with the dihedral angles which the foregoing analysis assigns - inconveniently - to *each* of the isomers. Stereostructure **2** was therefore only established by X-ray crystallography [23] of its *p*-nitrobenzoate **15** [24] (Fig. 1).

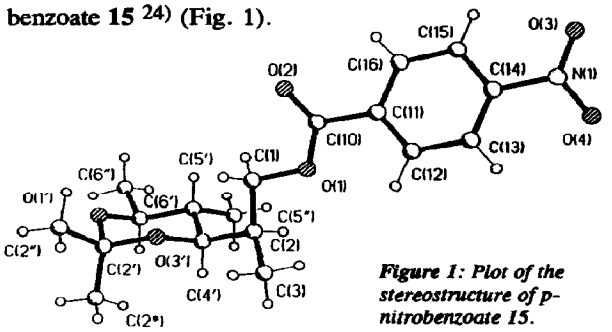



*Figure 1: Plot of the stereostructure of p-nitrobenzoate 15.*

**ACKNOWLEDGMENT**: We are indebted to *Schering AG* and *Chemetall AG* for donations of DIBAH and BuLi, respectively. *Prof. W. König* (Universität Hamburg) kindly measured enantiomeric excesses by GLC. Financial support of this work by the *Fonds der Chemischen Industrie* is greatly appreciated.

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23. Stoe-Siemens four circle diffractometer; Mo $K_\alpha$ radiation; refinement with SHELXL-92, R1 = 0.0978, wR2 = 0.2418. **15** crystallizes in $P2_12_12_1$ with $a$ = 599.4(3), $b$ = 778.8(6), $c$ = 4060.0(3) pm.
24. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-58607, the names of the authors, and the journal-citation.


(*Received in Germany* 7 *July* 1994; *accepted* 12 *August* 1994)