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The Sulfinyl Moiety as an Internal Nucleophile. 2. Stereoselective Synthesis of (−)-Galantinic Acid via 1,3-Asymmetric Induction†

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Abstract: A stereoselective synthesis of (−)-galantinic acid is disclosed. The key steps include hydrolytic kinetic resolution of a racemic epoxide and regio- and stereoselective heterofunctionalization of an olefin, using a pendant sulfinyl group as the nucleophile. The participation of the sulfinyl group was unambiguously proven by conducting the reaction in the presence of $H_2{}^{18}O$.

(−)-Galantinic acid (**1**), a nonproteinogenic amino acid, is a constituent of the peptide antibiotic galantin I, which was isolated from the culture broth of *Bacillus pulvifaciens*.[1] Galantinic acid was isolated from galantin I by chemical degradation and was originally assigned the structure **2**. The structure of galantin I and galantinic acid were revised by Ohfune and co-workers, who also reported the first synthesis of galantinic acid.[2a,b] Galantinic acid has attracted the attention of synthetic chemists due to its interesting biological activity and unique structure. The syntheses of galantinic acid reported to date[2] employ chiral pool starting materials (L-serine and D-ribonolactone); the 1,2-asymmetric induction in the vicinal amino alcohol formation and/or 1,3-asymmetric induction in the diol formation, however, needs to be improved. In connection with our interest in the use of the sulfinyl moiety as an intramolecular nucleophile,[3] we envisaged (Scheme 1, retrosynthetic analysis) the synthesis of galantinic acid from β-hydroxy-δ,ϵ-unsaturated sulfoxide (**5**). Galantinic acid can be elaborated from epoxide **3** by a one-carbon homologation by cyanide ion opening followed by hydrolysis. The epoxide can be elaborated from sulfoxide **4**, the synthesis of which can be traced to olefin **5**. Sulfoxide **5** can be readily elaborated from epoxide **6**.

Herein we report the details of our investigation that culminated in a stereoselective synthesis of a protected derivative of galantinic acid. Hydrolytic kinetic resolution[4] of the racemic epoxide **6**[5] with (*S*,*S*)-salen Co(III)-OAc catalyst afforded optically pure epoxide **8**[6] in 42.5% yield along with diol **7** (49%) which were readily separated.[7] Triethylamine-promoted opening of epoxide **8** by thiophenol afforded the homopropargyl alcohol **9**. Deprotection of the *p*-methoxybenzyl group with DDQ[8] and subsequent reduction of the resulting propargyl alcohol **10** with $LiAlH_4$[9] afforded trans allyl alcohol **11**, which was protected as its silyl ether **12**. Oxidation of sulfide **12** with $NaIO_4$[10] yielded an equimolar, inseparable mixture of sulfoxides **5** (Scheme 2).

Treatment of the epimeric mixture of sulfoxides **5** with *N*-bromosuccinimide (NBS) in the presence of water in toluene as the solvent afforded bromohydrin **13** as an inseparable mixture of epimeric sulfoxides. Oxidation of **13** with *m*-CPBA yielded sulfone **14**, which revealed a single set of signals in its ^{1}H NMR spectrum, proving unambiguously the isomeric nature of **13** as an outcome of the sulfur chirality. The structure of bromohydrin **13** was proven by transforming **14** into acetonide **17** employing a straightforward sequence of reactions (Scheme 3). Thus di-deprotection of the silyl ether followed by selective monoprotection of the primary hydroxy group of triol **15** as its *tert*-butyldiphenylsilyl (TBDPS) ether and reaction of resulting diol **16** with 2,2-dimethoxypropane (2,2-DMP) in the presence of catalytic amounts of camphor-10-sulfonic acid (CSA) afforded acetonide **17**. The ^{13}C spectrum of **17** revealed signals for the methyl group at δ 19.5, 29.3 and for the quaternary carbon at δ 99.3, indicating a 1,3-syn disposition of the hydroxy groups.[11] The anti disposition of the bromine and hydroxy groups is expected from an overall trans addition of the electrophile and nucleophile across the face of the double bond.[12]

The formation of **13** from **5** can be rationalized by bromonium ion attack on the olefin followed by intramolecular nucleophilic attack by the sulfinyl group in a 6-exo fashion to yield the sulfoxonium salt and finally hydrolysis[13] (Figure 1). The observed stereoselectivity can be explained by the difference in the energies of diastereomeric intermediates **I** and **III** (**II** not being preferred for

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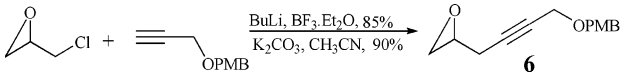
(5) The racemic epoxide **6** was readily prepared in two high-yielding steps: (i) reaction of propargyl ether with epichlorohydrin, using Yamaguchi protocol, and (ii) treatment of the resulting chloro alcohol with K_2CO_3 in CH_3CN.



6

(6) The alcohol **9** was transformed into its mandelate ester by reaction with (*S*)-α-methoxy mandelic acid and found to be homogeneous by comparing it with the ester prepared from racemic **9**. The absolute configurations of the product were determined by application of the models for the HKR reaction and by total synthesis.

(7) Attempted kinetic resolution of the epoxide **6,** using 0.55 equiv of PhSH in the presence of (*R*,*R*)-salen Co(III)OAc catalyst, afforded only racemic product **9**.

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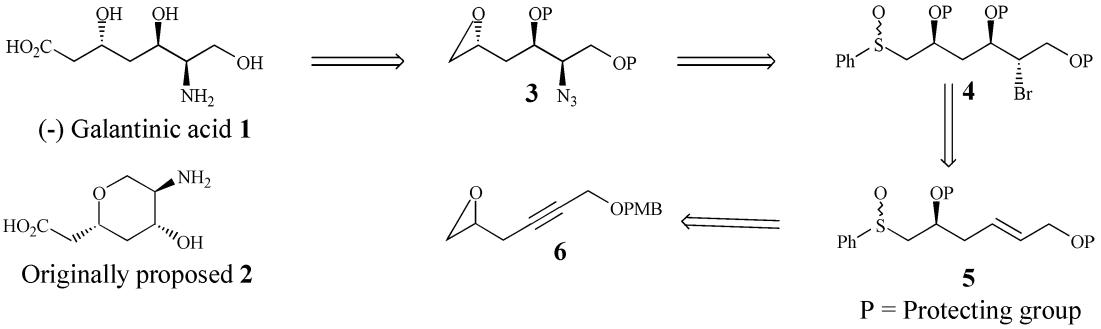
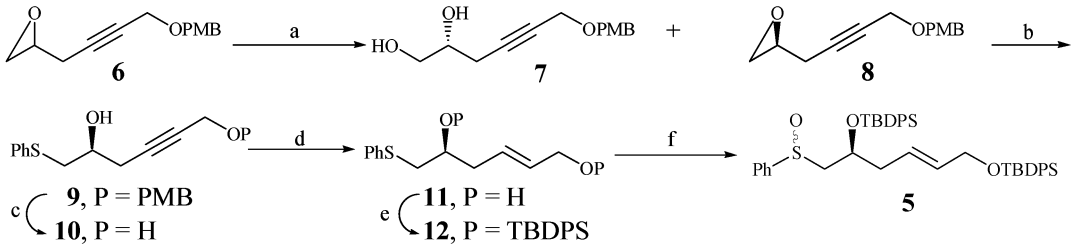
SCHEME 1

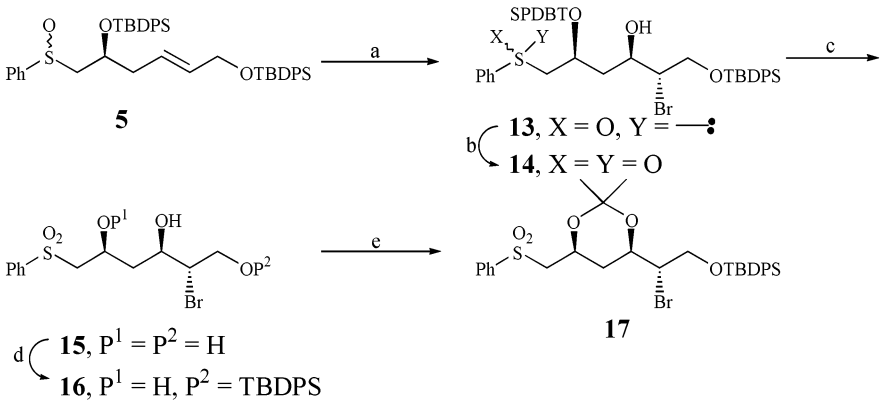


SCHEME 2[a]



[a] Reaction conditions: (a) (*S*,*S*)-salen Co(III)OAc catalyst, H_2O, THF, rt, 42.5% of **8** and 49% of **7**; (b) PhSH, Et_3N, CH_3CN, rt, 85%; (c) DDQ, CH_2Cl_2/H_2O (19:1), rt, 80%; (d) $LiAlH_4$, THF, 60 °C, 78%; (e) TBDPS-Cl, Imd., CH_2Cl_2, rt, 96%; (f) $NaIO_4$, THF, MeOH, H_2O, rt, 85%.

SCHEME 3[a]



[a] Reaction conditions: (a) NBS, toluene, H_2O, rt, 75%; (b) *m*-CPBA, CH_2Cl_2, rt, 90%; (c) *n*-Bu_4NF, AcOH, THF, rt, 70%; (d) TBDPS-Cl, Imd., CH_2Cl_2, rt, 90%; (e) 2,2-DMP, CSA, rt, 90%.

steric reasons in comparison to **III**) resulting from sulfoxide **5a**. The intermediate **I** is expected to be favored for steric reasons and the 1,3-anti product is expected to be formed. However, the reaction practically proceeds exclusively via intermediate **III** to yield the 1,3-syn product (**13a**). This is most likely due to a stereoelectronic effect probably arising due to the OTBDPS group being perpendicular[14] to the plane of the double bond complexed to the bromonium ion. Likewise the sulfoxide **5b** would react via intermediate **IV** to yield bromohydrin **13b**.

The nucleophilic attack by the sulfinyl moiety was undoubtedly proven by conducting the reaction of sulfoxide (**5**) with NBS in the presence of $H_2{}^{18}O$ to afford bromohydrin **18**. The acetyl derivative **19** revealed a $M^+ + 23$ signal at 879. Reduction of the sulfoxide afforded sulfide **20**, the mass spectrum of which revealed a $M^+ + 23$ signal at 861 proving that the ^{18}O label was incorporated on the sulfur oxygen (Scheme 4). The participation of the sulfinyl moiety is also proven by the fact that the epimeric sulfoxides react at different rates, one of them reacting within an hour with the other requiring ca. 16 h to react completely. It is therefore very clear that the homoallyl substituent alone influences the asymmetric induction and the sulfoxide configuration has no influence on the stereochemical outcome. It is also apparent that the asymmetric induction due to the OTBDPS group is greater than that from the OH or the OTBDMS (*tert*-butyldimethylsilyloxy) group, since the reaction of substrates, wherein the secondary hydroxy group in **5** is left unprotected or both the hydroxy groups are protected as the TBDMS ether, with NBS proceeds with inferior stereocontrol.

Bromohydrin **13** was elaborated to galantinic acid as depicted in Scheme 5. Selective deprotection of the primary silyl ether in **13** and treatment of the resulting

(14) For 1,3-syn asymmetric induction by a OTIPS group in the iodolactonization reaction see: Bedford, S. B.; Fenton, G.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1505.

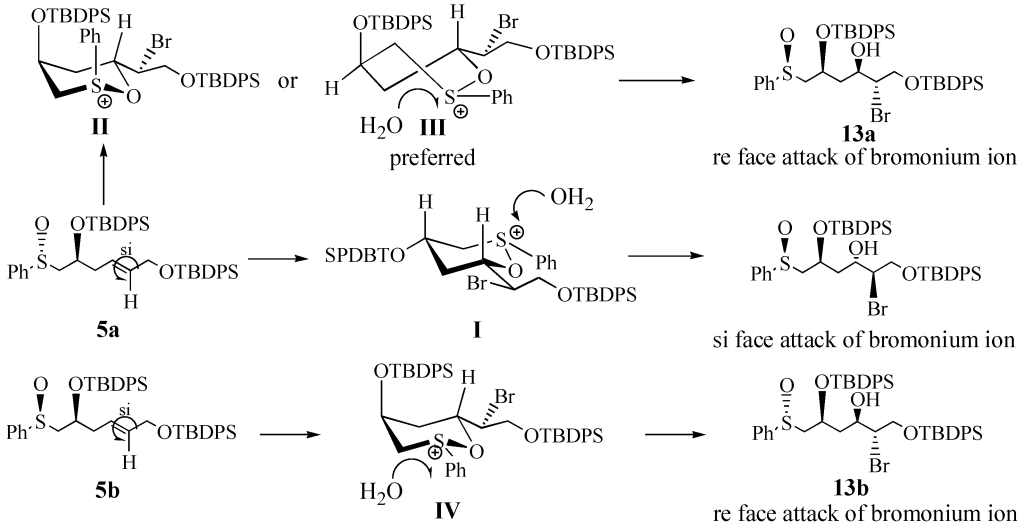
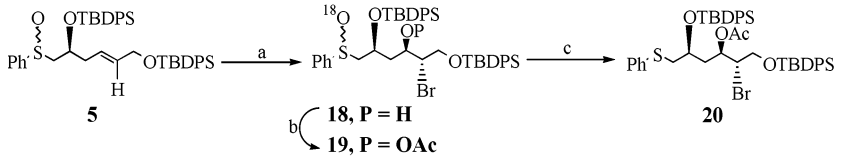


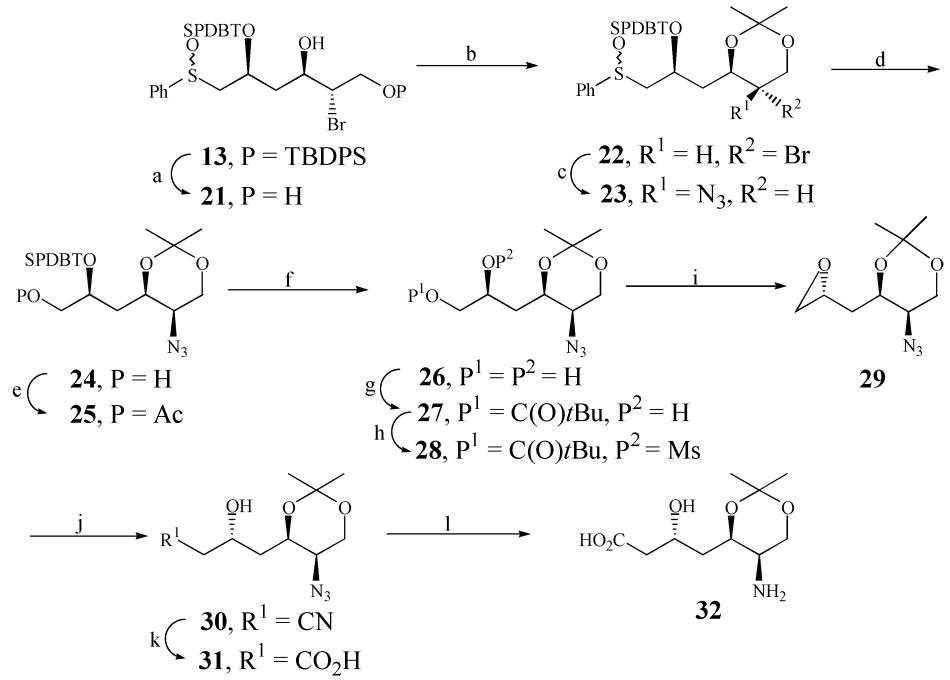
FIGURE 1.

SCHEME 4[a]



[a] Reaction conditions: (a) NBS, toluene, $H_2{}^{18}O$, rt, 75%; (b) Ac_2O, Et_3N, CH_2Cl_2, rt, 90%; (c) $(CF_3CO)_2O$, NaI, acetone, 0 °C, 75%.

SCHEME 5[a]



[a] Reaction conditions: (a) CSA, CH_2Cl_2/MeOH (1:1), rt, 78%; (b) 2.2-DMP, acetone, CSA, rt, 90%; (c) NaN_3, DMSO, 80 °C, 75%; (d) (i) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt, (ii) aq $NaHCO_3$, $NaBH_4$, 0 °C, 70%; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 80%; (f) *n*-Bu_4NF, AcOH, THF, rt, 70%; (g) pivaloyl-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (h) Ms-Cl, Et_3N, CH_2Cl_2, 0 °C; (i) 0.2 N NaOH, MeOH, 0 °C to rt, 65% overall yield for 3 steps; (j) NaCN, $Ti(O^iPr)_4$, *n*-Bu_4NI, DMSO, 70 °C, 80%; (k) 3 N NaOH, 30% H_2O_2, 70 °C, 1 h, 90 °C, 1 h, 70%; (l) H_2, Pd/C, MeOH, 80%.

diol **21** with 2,2-DMP in the presence of catalytic amounts of CSA afforded acetonide **22**. The ^1H NMR spectrum of **22** revealed a signal for the proton attached to the carbon bearing bromine atom at δ 4.10 with a coupling constant equal to 9.0 Hz, proving the anti disposition of the bromine and hydroxy group in **13**. The reaction of sulfoxide **5** with NBS thus proceeds regio- and stereospecifically.

Displacement of the bromide by an azide yielded acetonide **23**, which was subjected to Pummerer rear-

rangement[15] and reduction of the resulting aldehyde in the same pot to yield alcohol **24**, which was characterized as its acetate derivative **25**. The next stage in the reaction sequence called for the inversion of the hydroxy group protected as its silyl ether, which was achieved by a four-step sequence as detailed below. Thus deprotection of **24** afforded diol **26**, which was subjected to selective protection to yield the pivalate ester **27**. The crude product[16] was subjected to mesylation to yield **28**. Hydrolysis of the pivalate ester led to concomitant displacement of the mesyl group to afford epoxide **29** with an inversion of configuration. The epoxide was opened with sodium cyanide, using Sharpless protocol[17] to yield the β-hydroxy cyano compound **30**. Hydrolysis of the cyano group by treatment with aq alkaline hydrogen peroxide[18] yielded the β-hydroxy acid **31**. Reduction of the azido moiety in **31** with 5% Pd/C under an atmosphere of hydrogen afforded the protected galantinic acid derivative **32**.

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(16) Attempted purification of the pivalate ester by column chromatography led to a partial migration of the pivalate to the secondary hydroxyl group as understood from the ^{1}H NMR, which revealed a multiplet at δ 5.1.

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(18) Frye, S. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402.

In summary, we have disclosed a highly stereoselective route to a protected galantinic acid derivative in 12 steps (5.6% overall yield) from sulfoxide **5**. The key steps include a hydrolytic kinetic resolution of a racemic epoxide and heterofunctionalization of an olefin by a pendant sulfinyl group as the nucleophile with efficient 1,3-asymmetric induction. The methodology described herein would prove useful in the synthesis of a wide variety of target molecules possessing a 1,3-syn/anti diol functionality.

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Supporting Information Available: Experimental details for the preparation of compounds **5**, **8**−**17**, **20**−**26**, and **29**−**32** (including analytical data) and copies of ^{1}H NMR spectra of all the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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