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An asymmetric synthesis of (2*S*,3*S*)-safingol

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Abstract—Two efficient asymmetric syntheses of (2*S*,3*S*)-safingol have been developed starting from easily available (*R*)-cyclohexylideneglyceraldehyde. The key steps in the syntheses were a diastereoselective addition of a suitable alkylmagnesium or lithium reagent, and simple organic transformations. Compared to earlier syntheses, the route involving alkyllithium addition is more viable practically due to its excellent diastereoselectivity, use of inexpensive materials/reagents and operational simplicity.

The amino alcohol, (2*S*,3*S*)-2-amino-1,3-octadecanediol (safingol, **1**) is valued as an antineoplastic and antipsoriatic drug.[1] The compound is being extensively investigated for its role in cell regulation, signal transduction,[2] and inhibition of protein kinase C.[3] Several syntheses of **1** based on diastereoselective or enantioselective methods[4a–d] and resolution[5a–d] have been reported. These include methods based on enantioselective Henry reaction[4a] and ketone reduction,[4b] a multistep synthesis from (*Z*)-2-buten-1,4-diol,[4c] and a diastereoselective synthesis using a suitable chiral oxazolidinyl ester.[4d] In spite of their elegance, some of these methods[4a,d] use reagents that are either expensive or that are prepared via several steps. Thus, the primary aim of the present work was to develop a selective and efficient synthesis for the medicinally important compound (2*S*,3*S*)-**1**.

Earlier, we showed[6a] that the addition of Grignard reagents to cyclohexylideneglyceraldehyde **2** provides an easy access to the C-3 epimers of alkanetriol derivatives, which are useful chirons for the synthesis of various classes of bioactive compounds.[6b,c] Consequently, we explored a similar approach using aldehyde **2** for the synthesis of **1** (Scheme 1). The reaction of pentadecylmagnesium bromide with **1** proceeded with a good diastereoselectivity (*syn*:*anti* 22:78) to give the *syn*- and *anti*-carbinols **3a** and **3b** in a good yield. The *syn*- and *anti*-stereochemistry of easily isolated diastereomers **3a** and **3b** was confirmed by comparing the ^{1}H NMR resonances of the CH_2O and CHO groups with those reported in the literature.[7a,b] Protection of the hydroxyl group of **3b** by silylation gave **4** which following deacetalization via a new neutral protocol ($CuCl_2{\cdot}H_2O$/MeOH) furnished diol **5**. After regioselective monosilylation of the primary hydroxyl, the resultant compound **6** was converted to azide **7** with diphenylphosphoryl azide in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine. The reduction of the azide function of **7** with lithium aluminium hydride (LAH) directly afforded the target compound **1** via concomitant desilylation.

Having completed the above synthesis, we ventured towards a more practicable synthesis of **1**. For this, it was essential to (i) develop a better enantioselective route for **3b**, and (ii) use inexpensive reagents for the introduction of the required amine function, reagents such as Ph_3P, $(PhO)_2P(O)N_3$, TPSCl, TBSCl and DEAD being deemed too expensive. Aldehyde **2** was reacted with freshly prepared *n*-pentadecyllithium in hexane to give carbinols **3a** and **3b** with vastly improved *anti*-selectivity (**3a**:**3b**, 6:94). Deacetalization with 2% methanolic HCl furnished triol **8**, which was converted into acetal **9** under solvent-free conditions. Tosylation followed by reaction with NaN_3 furnished azide **10** along with a small amount (9%) of the elimination product. Catalytic hydrogenation of **10** and subsequent acidic hydrolysis afforded **1** (Scheme 2).[8]

Amongst the existing syntheses of **1**, the recent multigram scale synthesis[5d] appears most attractive. However, as a resolution-based method, it has its own

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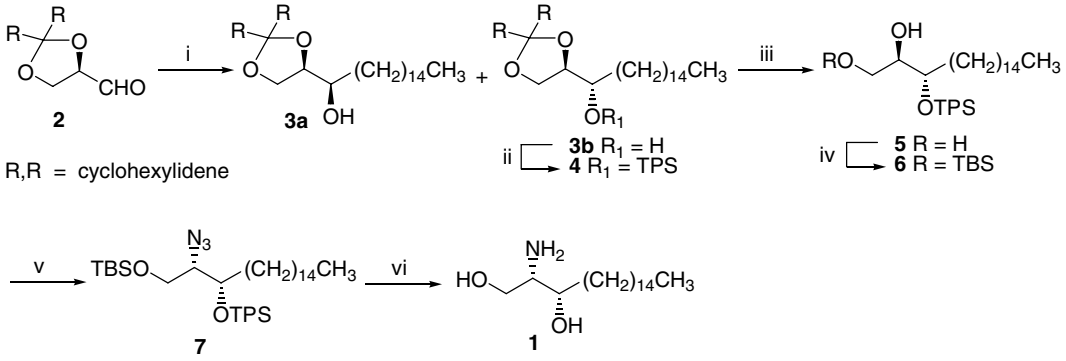
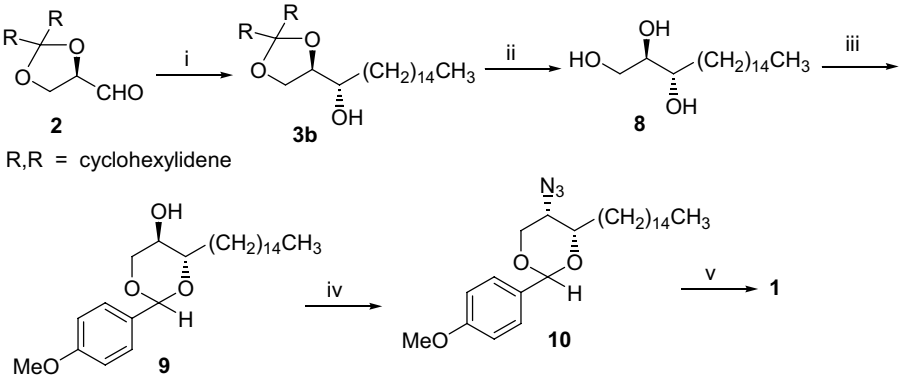


Scheme 1. Reagents and conditions: (i) $CH_3(CH_2)_{14}MgBr$, THF, rt (86%); (ii) *tert*-butyldiphenylsilyl chloride (TPSCl), imidazole, CH_2Cl_2, rt (93%); (iii) $CuCl_2{\cdot}H_2O$, MeOH, Δ (81%); (iv) *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, CH_2Cl_2, rt (88%); (v) Ph_3P, $(PhO)_2P(O)N_3$, DEAD, THF, 0 to rt (84%); (vi) LAH, diethyl ether, reflux (77%).



Scheme 2. Reagents and conditions: (i) $CH_3(CH_2)_{14}Br$, Li, hexane, −40 °C (89%); (ii) MeOH, HCl, rt (91%); (iii) *p*-anisaldehyde, HCl, rt (81%); (iv) *p*-TsCl, pyridine, CH_2Cl_2, −5 °C, NaN_3, DMF, Δ (75%); (v) H_2, 10% Pd–C, EtOH, rt, aqueous HCl (72%).

limitations, especially for the generation of the enantiomer. Further, it required a laborious standardization of the Henry reaction for the synthesis of the required diastereomeric nitro carbinol, the precursor for **1**. In comparison, the present method is operationally simple and the reagents and starting material are readily available. The starting aldehyde **2** can be easily prepared in appreciable amounts from the inexpensive (D)-mannitol. We have standardized its synthesis on a 170 g scale and used it for the syntheses of various bioactive compounds.[9a–c] Both the Grignard or alkyllithium reaction and azidation are amenable to scale-up. The second procedure involving five synthetic steps is reproducible and provided **1** in ~35–37% overall yield starting from **2**. Given that (*S*)-**2** is also available easily from vitamin C,[10] the flexibility of our method would allow the preparation of any desired isomer of **1** with an equal efficiency.

References and notes

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