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AN EFFICIENT SYNTHESIS OF (2S,3R)- AND (2S,3S)-SPHINGOSINE

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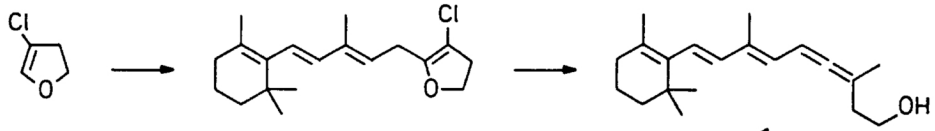
A straightforward sequence of reactions allows the conversion of D(+)-Mannose and D(+)-ribono-1,4-lactone into "erythro"-(2S,3R)- and "threo"-(2S,3S)-sphingosine, respectively.

Metals or organometallics can promote a ring-opening reaction of 2,3-dihydrofurans that gives rise to 3-hydroxyacetylenes or 3-hydroxyallenes.[1] For example, consecutive treatment of 4-chloro-2,3-dihydrofuran with butyllithium, copper iodide, β-ionylideneethyl bromide, methyllithium (2 equivalents), and water affords the "isoretinol" **1** .[2]



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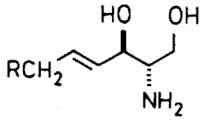
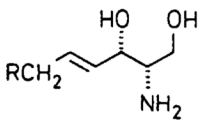
Extended to sugar-derived dihydrofurans, such ring-opening reactions should make many new chiral building blocks readily available. We wanted to demonstrate the practical potential of this approach by applying it to the synthesis of natural sphingosine ("erythro"- **2** ; mp 83.0 - 83.5 °C; triacetate : mp 105 - 106 °C), the most prominent constituent of membrane lipids, as well as its (3S)-epimer ("threo"- **2** ; mp 88.0 - 88.5 °C; triacetate : mp 43.0 - 43.5 °C). In both synthetic sequences (see schemes on the next two pages) particularly inexpensive starting materials, D(+)-mannose and D(+)-ribono-1,4-lactone,[3] were employed and a diastereomerically different, but otherwise identical 4-bromo-3-methoxymethoxy-2-methoxymethoxymethyl-2,3-dihydrofuran served as the key intermediate.

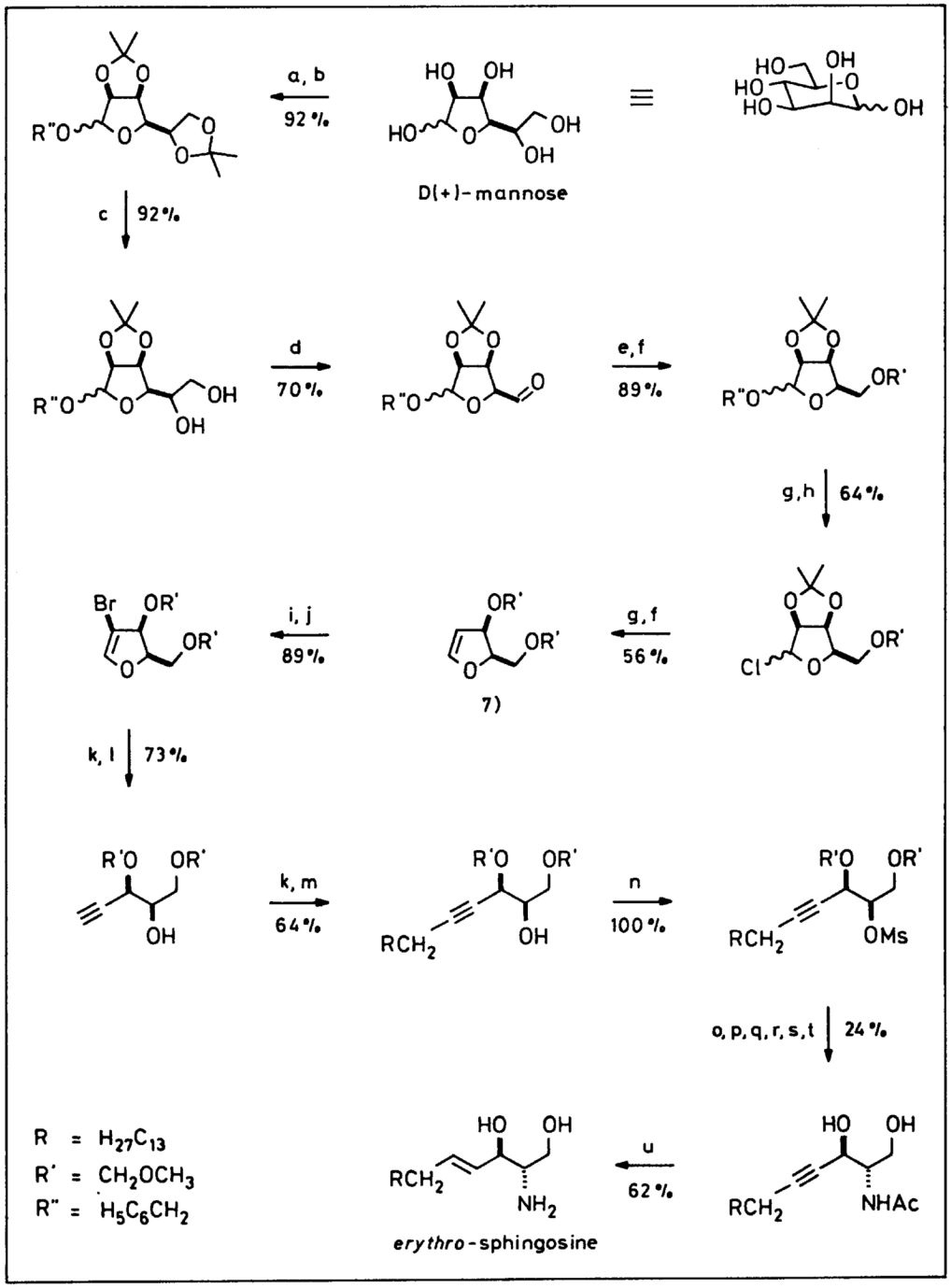


R = $H_{25}C_{12}$

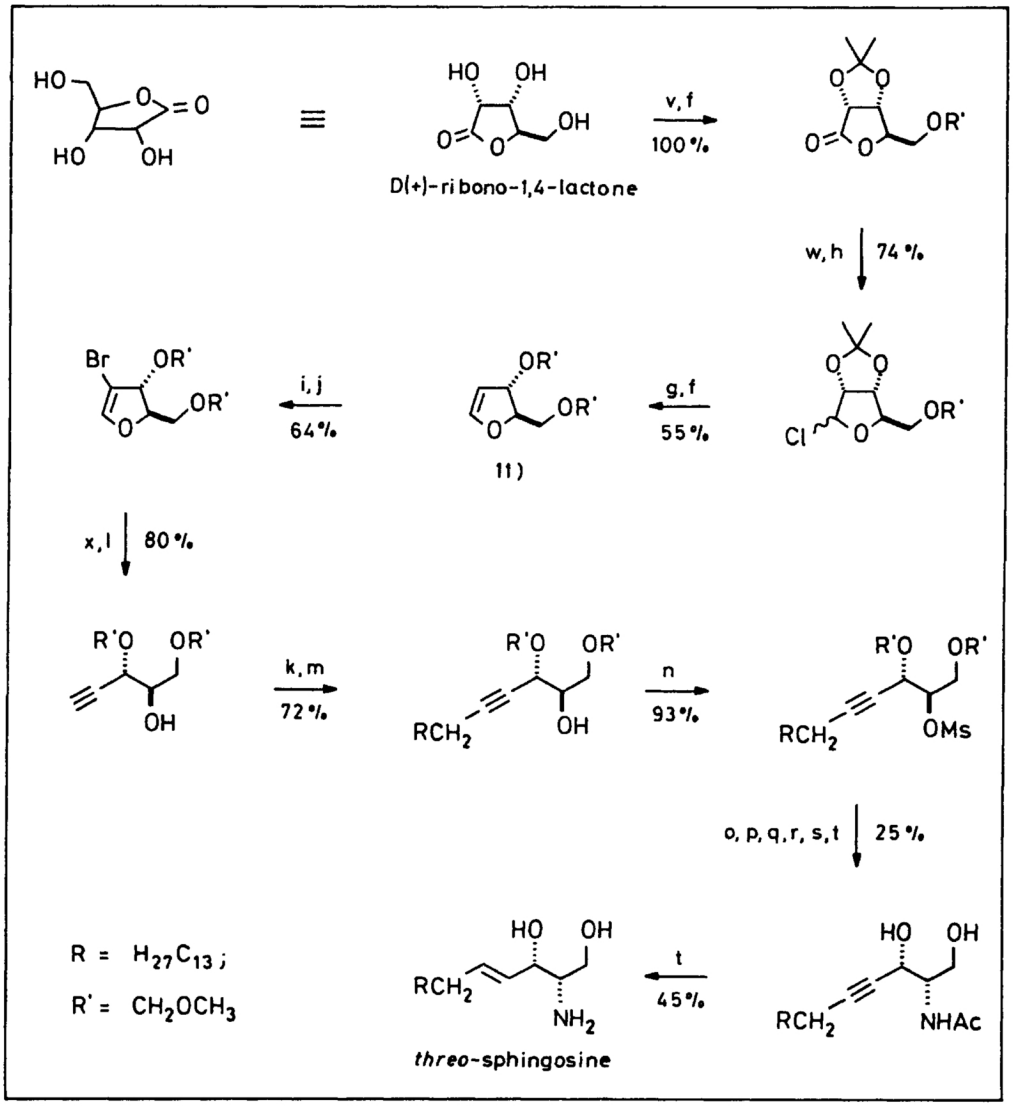


erythro- **2** (2S,3R)

threo- **2** (2S,3S)



a) $(H_3C)_2CO/H^+$ [4]; b) $NaH/ClCH_2C_6H_5/DMF$ (DMF = N,N-dimethylformamide) [5]; c) HCl/aq. $HOCH_3$ [5]; d) $NaIO_4/HOCH_3$ [5]; e) $NaBH_4/HOC_2H_5$ [5]; f) $ClCH_2OCH_3$ [6]/ $H_5C_2N(^iC_3H_7)_2$ [7]; g) Li/NH_3 [7]; h) $CCl_4/P(C_6H_5)_3$ [7]; i) Br_2/CCl_4; j) DBU/ THF (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; THF = tetrahydrofuran); k) LiC_4H_9/ THF; l) H_2O; m) $BrCH_2R$/HMPT (R = $C_{12}H_{25}$; HMPT = hexamethylphosphoric triamide); n) $ClSO_2CH_3/H_5C_2N(^iC_3H_7)_2$; o) LiN_3/DMF [8]; p) $P(C_6H_5)_3$/toluene (115 °C) [9]; q) $(H_3CCO)_2O/H_5C_2N(^iC_3H_7)_2$; r) H_2O (100 °C); s) $BrSi(CH_3)_3$ (-30 °C) [10]; t) $NaHCO_3/H_2O$ [10]; u) Na/HOC_4H_9 (120 °C); v) $(H_3C)_2C(OCH_3)_2/(H_3C)_2CO/H^+$ [7]; w) $HAl(CHCH_3C_2H_5)_2/(H_5C_2)_2O$ [7]; x) $LiCHCH_3C_2H_5$/THF.



Despite their length we believe these new syntheses to present major advantages when compared with existing routes leading to sphingosines [12] and related compounds : [13]

- All reaction steps may be performed on a large scale (e.g., using 2 mol of starting material).
- In general, the yields are quite satisfactory and, moreover, may be still substantially improved by modifications, simplifications, and shortcuts.
- On the basis of HPLC- and NMR-evidence, the occurrence of epimerization (and, a fortiori, racemization) to any substantial degree can be ruled out in the present case. In contrast, the stereochemical integrity of final products may not be assured if, though quite elegantly, stereocontrol is achieved by asymmetric induction.[12h] Stereochemical integrity is again not assured beyond any doubt

if enantiomerically pure starting materials (e.g., D-glucose [12d] or L-serine [12e]) are employed but if in the later course of the reaction sequence intermediates having formyl-bearing chiral centers are involved and get exposed to basic reagents. On the other hand, methods lacking enantio- or diastereoselectivity are inevitably restricted to the small-scale preparation of samples since they require high performance separation techniques.[12f,g]

- The strategy of assembling sphingosine or derivatives thereof by putting together the polar head-group, "carved out" from a sugar precursor, and a fatty acid side-chain in a very late stage provides a maximum of synthetic flexibility. This approach should prove to be quite useful for the preparation of isotopically labelled or heterosubstituted sphingolipids, work in which we are presently engaged.

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