

SYNTHESIS OF *meso*- AND *dl*-2,2'-METHYLENEBIS[TETRAHYDRO-2-FURANMETHANOL]. POTENTIAL BUILDING BLOCKS FOR THE CONSTRUCTION OF IONOPHORES HOUSING SPIROTETRAHYDRO-FURANYL MOTIFS[‡]

Leo A. Paquette,* Brian A. Stearns,[†] Pamela A. Mooney,[†] and Jinsung Tae

Evans Chemical Laboratories, The Ohio State University, Columbus, OH 43210, USA

Abstract - A seven-step route to diols (**1**) and (**2**) is described, along with a pathway for achieving incorporation of the aliphatic chain of **2** into a cyclohexane core.

Despite the fact that many classes of ionophoric ethers have already been described,¹ numerous new molecular constructs remain to be prepared and evaluated for their ability to function as three-dimensional cation binders. In recent years, increasing attention has been paid to structural types that possess high rigidity in order to skirt the need for conformational reorganization prior to complexation. In consideration of the fact that tetrahydrofuran rings exhibit a nearly ideal atomic distribution for solubility in both aqueous and organic solvents, we have concerned ourselves with the development of synthetic routes to belted polyspirotetrahydrofuran arrays² of diverse type.³ The present study details a convenient approach to the stereoisomeric diols (**1**) and (**2**), and provides an example as to how these potentially useful building blocks can be transformed into an architecturally more complex structure.

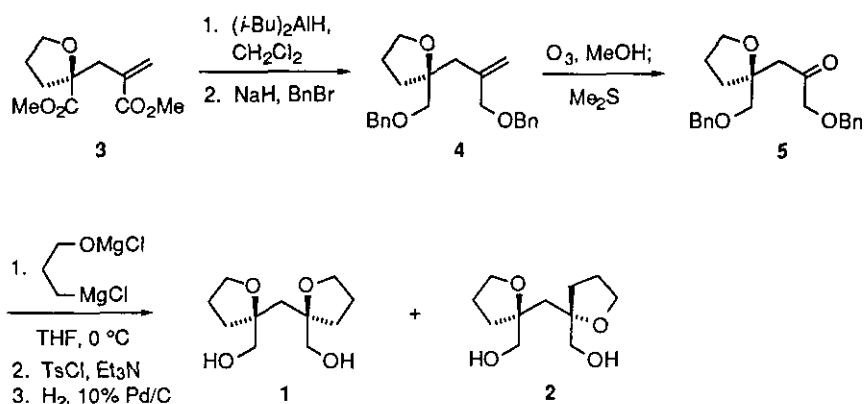


The route to **1** and **2**, which began with the alkylation of methyl tetrahydrofuran-2-carboxylate⁴ with methyl α -(bromomethyl)acrylate⁵ to give **3** (73%), made recourse to subsequent Dibal-H reduction and *O*-benzylation to deliver **4** (Scheme 1). Ozonolytic cleavage of the double bond provided ketone (**5**) (>90% based on unconsumed **4**) and set the stage for introduction of the second tetrahydrofuran ring by utilization of the Normant reagent.⁶ Once formation of the 1,2-adduct had been achieved (82%), cyclization was accomplished under conventional tosylation conditions (75%), and the benzyl groups were cleaved by

[‡]Undergraduate research participants.

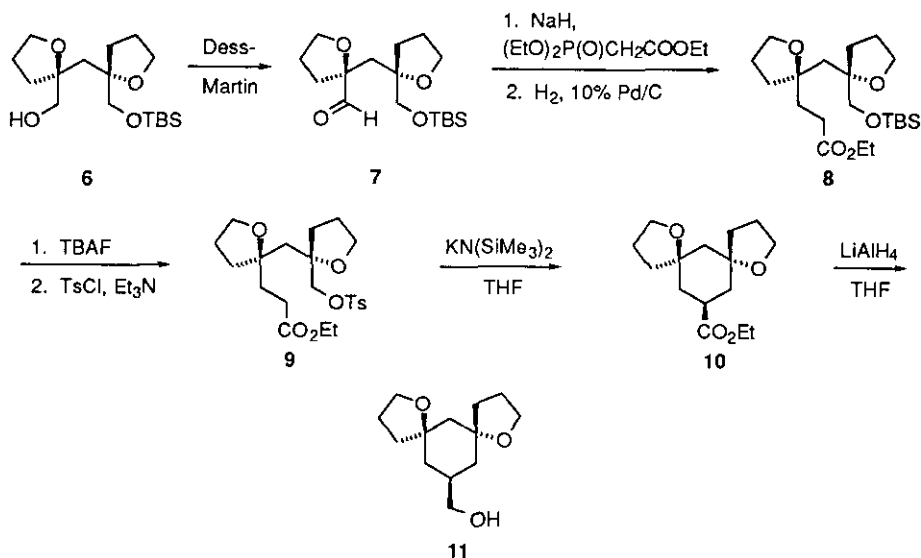
hydrogenolysis (89%). Following the chromatographic separation of **1** from **2**, these isomers were distinguished by twofold esterification with (*R*)-(-)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride.⁷ The Mosher diester which resulted from the less polar of the two diols gave two sets of ¹³C NMR peaks. The other did not. On this basis, **1** was deduced to be the more polar diastereomer.⁸

Scheme 1



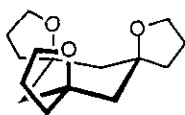
Although the dimesylate of **1** could be generated without difficulty, attempts to produce the diiodide therefrom was unsuccessful. When other attempts to implement $\text{S}_{\text{N}}2$ displacements on this very hindered intermediate were to no avail, recourse was made instead to a strategy based on intramolecular alkylation. Thus, the monoprotected alcohol (**6**) was oxidized to aldehyde (**7**) in a modest 40% yield with the Dess-Martin periodinane⁹ (Scheme 2). Chain extension within **7** was realized through application of Wadsworth-Emmons technology and subsequent hydrogenation of the resulting α,β -unsaturated ester to give **8** (49%

Scheme 2

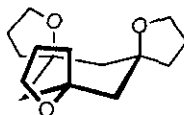


over both steps). Exposure of **8** to tetra-*n*-butylammonium fluoride unmasked the hydroxyl group (86%), making possible purposeful conversion to the multifunctional tosylate (**9**) (67%). When this advanced intermediate was treated with potassium hexamethyldisilazide, the anticipated cyclization¹⁰ materialized, but the process proved to be inefficient (~20% yield) on small scale. The structural assignment to **10** was confirmed by hydride reduction to carbinol (**11**) (98%) which was independently synthesized by another route.¹¹

Although the chemistry defined herein might be exploited for the synthesis of trispiro ethers (**12**) and (**13**), the inefficiencies associated with several of the steps suggest that a better option would involve the



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elaboration of spirotetrahydrofuran rings on a preformed cyclohexane core. We hope to be in a position to report on this alternative tactic in the near future together with a comparative analysis of the chelating abilities of these trispiro ethers.

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