

Asymmetric Synthesis of 1,3-Dialkyl-Substituted Carbon Chains of any Stereochemical Configuration by an Iterable Process

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Dedicated with respect, admiration, and fond best wishes to Professor E.J. Corey.

Abstract: A highly practical, iterable method for the preparation of 1,3,5,*n*(odd)-polyalkyl-substituted carbon chains based upon the asymmetric alkylation of pseudoephedrine amide enolates is described.

Carbon chains with "skipped" or 1,3-dialkyl substituents and, in particular, 1,3-dimethyl groups, are common structural elements within many biologically active natural products. Examples include the antibiotic ionomycin, the immunosuppressant rapamycin, and the squalene synthase inhibitor zaragozic acid A. A concise strategy for the asymmetric synthesis of such systems which, by iteration, could be extended to any series of 1,3,5,*n*(odd)-polyalkyl-substituted carbon chains was proposed by Evans et al. in their synthesis of ionomycin.¹ They pointed out that a sequence involving the asymmetric alkylation of a chiral propionate-derived enolate, reduction of the product to a primary alcohol and alcohol activation (e.g., $\text{RCH}_2\text{OH} \rightarrow \text{RCH}_2\text{I}$), followed by a second alkylation reaction with a chiral propionate-derived enolate, would provide an iterable approach to the synthesis of 1,3,5,*n*-polymethyl-substituted carbon chains. Although conceptually straightforward, the implementation of such a strategy in an efficient and practical manner constitutes a demanding challenge in synthetic methodology. Part of the difficulty arises from the inherently poor reactivity of β -branched electrophiles in alkylation reactions. Alkylations with (*S*)-prolinol-derived amide enolates typically employ the carcinogenic hexamethylphosphoric triamide (HMPA) as an additive.² Imide-derived enolates do not react with β -branched alkyl iodides³ and, although a recent report demonstrated that they do react with β -branched alkyl triflates, a large excess of the electrophile (25 equiv) was used in the reaction.⁴ This is an undesirable feature in an iterative sequence, where the electrophilic component becomes successively more valuable with each iteration. Nicolaou et al. have effectively employed Enders' chiral hydrazone enolate alkylation methodology⁵ for the synthesis of the dimethyl-substituted carbon side-chain of zaragozic acid A,⁶ but the expense of the chiral auxiliary would be prohibitive to large-scale applications of this methodology. In conjunction with investigations into the use of pseudoephedrine as a chiral auxiliary for the asymmetric alkylation of carboxylic acid derivatives, we have developed and report herein an exceedingly efficient and practical implementation of an iterable alkylation strategy for the enantio- and diastereoselective preparation of 1,3,5-trimethyl-substituted carbon chains of all possible configurations.

In prior work, we have demonstrated that pseudoephedrine serves as a highly practical chiral auxiliary for the asymmetric alkylation of a wide variety of its carboxamide derivatives.⁷ Pseudoephedrine is selectively *N*-acylated in high yield and enolate derivatives of the amide products, obtained by deprotonation of the amide with lithium diisopropylamide (LDA) in tetrahydrofuran in the presence of 6 equiv of lithium chloride ($-78 \rightarrow 23^\circ\text{C}$),⁸ react efficiently and highly diastereoselectively with alkyl iodides. In this work, we show that the high stereoselectivity of these alkylation reactions is essentially unaffected when chiral β -branched alkyl iodides are employed in the reaction. Furthermore, we introduce a modified protocol for the reduction of the alkylation products with lithium amidotrihydroborate⁹ (LiH_2NBH_3 , LAB) that greatly facilitates the isolation and purification of the product alcohols. Transformation of each alcohol to the corresponding iodide then allows for iteration of the process, as shown below.

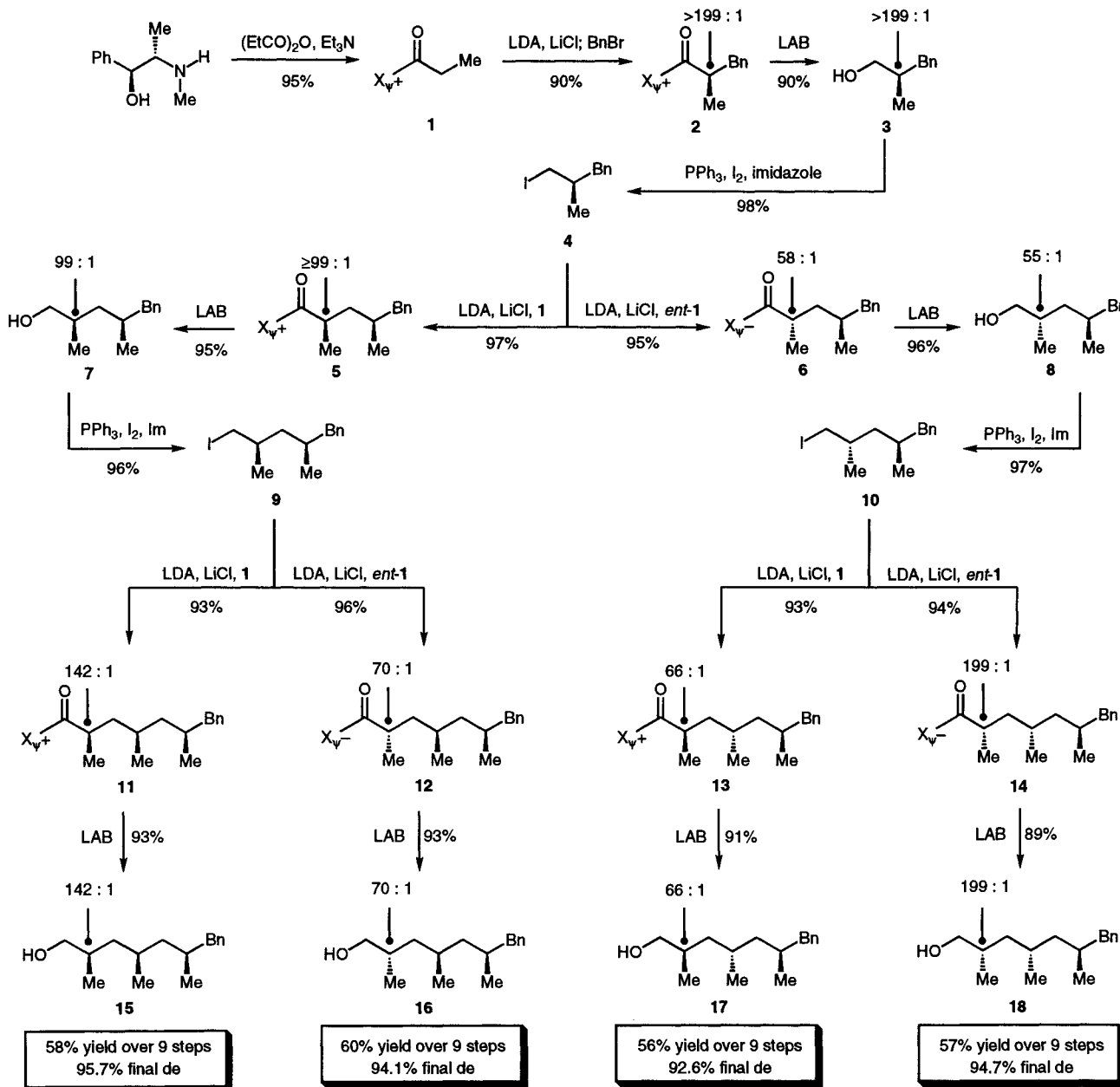
Pseudoephedrine propionamide **1** was prepared in 95% yield by crystallization of the crude product from an acylation mixture comprising pseudoephedrine (1 equiv), propionic anhydride (1.07 equiv), and triethylamine (1.20 equiv, dichloromethane as solvent). Enolization of **1**, as described above, and alkylation at 0°C with benzyl

bromide (1.50 equiv) afforded the alkylation product **2** in 94% crude de and >99% de (90% yield) after recrystallization.¹⁰ Hereafter, all alkylations described employ excess enolate (1.3–1.8 equiv) and only 1 equiv of the more valuable alkyl iodide, and all de's reported reflect crude values with care taken to avoid adventitious diastereomeric enrichment upon purification. In general, reactions employing excess enolate (yield based on alkyl iodide) are higher yielding than those employing excess alkyl halide (yield based on enolate).

Reduction of amide **2** with LAB, prepared as previously described⁹ by deprotonation of commercial, crystalline borane-ammonia complex with *n*-butyllithium, proceeded well on small scale, but work-up and isolation of the product alcohol **3** on large scale was complicated by the presence of boronic esters of **3**, which were difficult to hydrolyze. This problem was traced to the formation of butylboron hydrides during the deprotonation reaction. Use of LDA as the base (3.9 equiv, 4.0 equiv of $\text{H}_3\text{N} \cdot \text{BH}_3$, $0 \rightarrow 23^\circ\text{C}$) avoided this problem entirely and LAB reductions proceeded efficiently independent of reaction scale. The modified procedure employed a simplified work-up involving an aqueous acidic extraction followed by flash column chromatographic purification. Reduction of substrate **2** with LAB (3.90 equiv), generated by the latter protocol, at 23°C for 1 h afforded alcohol **3** in 90% yield and >99% ee (determined by chiral HPLC analysis, Chiralcel OD). In this and all subsequent LAB reductions described, the stereoisomeric ratios of the product alcohols were the same as those of the starting amides, within the limits of detection by our analytical techniques.

Iodination of alcohol **3** by a modification of the method of Garegg et al.¹¹ afforded iodide **4** in 98% yield. Treatment of iodide **4** (1 equiv) with 1.8 equiv of the enolate derived from (*S,S*)-pseudoephedrine propionamide (**1**), prepared as described above, at 23°C for 6 h afforded the 1,3-*syn*-alkylated product **5** with >99:1 diastereoselectivity and in 97% yield.¹² Use of the enolate derived from (*R,R*)-pseudoephedrine propionamide (*ent-1*) under otherwise identical conditions provided the 1,3-*anti*-product **6** with 58:1 diastereoselectivity and in 95% yield. Thus, reactions producing the *syn*-stereochemistry appear to represent a matched case while those producing the *anti*-diastereomer represent a mismatched case.¹³ It should be emphasized that even the "mismatched" alkylation reaction is highly selective and, as further demonstrated in results reported below, the selectivity of these alkylation reactions is governed almost exclusively by the stereochemistry of the enolate, and not the alkyl halide.

Iteration of this sequence proceeded with similarly high efficiency and with slightly higher diastereoselectivities in the alkylation reactions (Scheme 1). Thus, reduction of amides **5** and **6** with 3.9 equiv of LAB provided alcohols **7** (95% yield) and **8** (96% yield), respectively, without detectable epimerization, within experimental error. Iodination of each product, as before, provided the corresponding iodides **9** (96% yield) and **10** (97% yield). Reaction of *syn*-iodide **9** (1 equiv) with 1.8 equiv of the enolate derived from **1** afforded the *syn,syn*-alkylation product **11** with 142:1 selectivity and in 93% yield, whereas the enolate derived from *ent-1* produced the *anti,syn*-product **12** with only slightly lower selectivity (70:1, 96% yield). Reaction of *anti*-iodide **10** with 1.8 equiv of the enolate derived from **1** produced the *anti,anti*-amide **13** with 66:1 selectivity and in 93% yield, whereas the enolate derived from *ent-1* proceeded with higher selectivity (199:1) to form the *syn,anti*-product **14** in 94% yield. These results support the idea that *syn*-products represent matched cases and *anti*-products mismatched cases and also that reaction diastereoselectivities increase with the steric bulk of the alkyl iodide. Reduction of each of the amides **11–14** with 3.90 equiv of LAB at 23°C provided the corresponding alcohols **15–18** in 89–93% yield. In each case, the diastereomeric ratio of the product was



Scheme 1

identical to the starting amide, within experimental error.

As detailed within Scheme 1, each of the products 15-18 was produced in an aggregate yield of >56% for the 9-step sequence starting from pseudoephedrine (average yield per step: 94%) and with a final de in excess of 92.6% (defined as per cent specified diastereomer minus the per cent of all contaminating diastereomers).¹⁴ The results serve to emphasize the exceptional diastereoselectivity and efficiency of the alkylation reactions of pseudoephedrine amide enolates and demonstrate a practical, iterable method for the preparation of 1,3,5,n-polyalkyl-substituted carbon chains of any desired configuration.

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- (10) Diastereomeric ratios of pseudoephedrine amides and primary alcohols were determined by chiral capillary GC analysis (Chirasil Val) of the corresponding acetate esters or trimethylsilyl ethers, with a detection limit of approximately 199:1.
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- (12) Using 1.8 equiv of enolate (0.19 M), typical reaction times were 6-7 h at 23 °C for the formation of products **5** and **6**, and 18 h at 23 °C for products **11-14**. Lesser amounts of enolate could be employed with longer reaction times. For example, the reaction of iodide **4** with 1.3 equiv of the enolate derived from **1** (0.19 M) proceeded to completion within 18 h at 23 °C (90% yield, 66:1 selectivity).
- (13) A similar observation was reported in alkylations of prolinol-derived enolates (see ref. 2b).
- (14) Base-line resolution of mixtures of the 4 diastereomers **15-18** was achieved by chiral capillary GC analysis of the corresponding acetate esters.