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Diastereoselective Conjugate Addition/Cyclization/Bromination: Access to Four Stereocenters in a Single Step

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Abstract

A stereoselective tandem conjugate addition reaction with a chiral amine-derived nucleophile is reported in which the enolate intermediate is quenched with 1,2-dibromotetrachloroethane as a mild brominating reagent. X-ray analysis of a subsequent derivative was used to prove the configuration at each of the four newly formed stereocenters. The resulting α-bromoester underwent selective transesterification catalyzed by mild base to allow selective manipulation of the two ester groups of the product.

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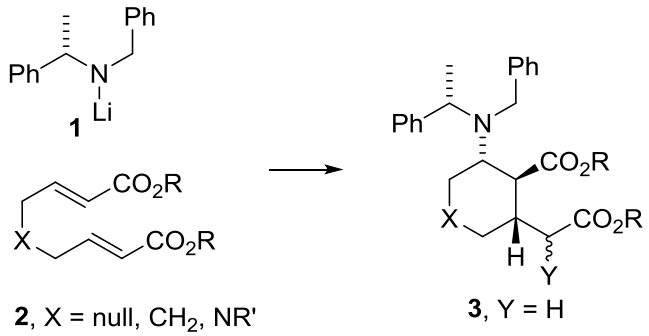
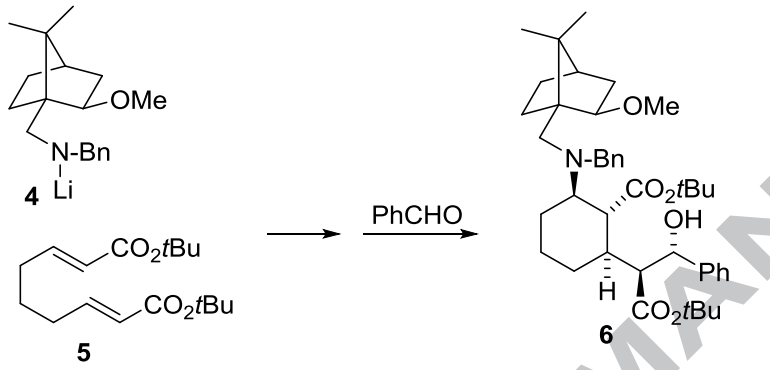
Keywords: Asymmetric synthesis; Conjugate addition; Electrophilic bromination

Introduction

The asymmetric conjugate addition of the α–methylbenzylamine-derived lithium amide **1** to a range of α,β-unsaturated esters has been widely used in the synthesis of β-aminoacid derivatives.[1] Tandem asymmetric conjugate addition/cyclization of a bis-α,β-unsaturated ester **2** initiated by **1** has been demonstrated for the synthesis of trisubstituted cyclopentane, cyclohexane, and piperidine derivatives **3** (Scheme 1).[2-6] The ready availability of both enantiomers of the chiral amine nucleophile allows access to either enantiomer of the product. In related work but using a chiral bornylamine-derived nucleophile **4**, the enolate from the cyclization step was trapped with an aldehyde electrophile to generate products **6** having two additional stereocenters (Scheme 2).[7] The enolate has been similarly trapped with a second Michael acceptor, with reaction occurring from the same face of the enolate as in the aldol trapping.[8] In simple conjugate additions to reactants having only one α,β-unsaturated ester group, the enolate has also been trapped with alkylating agents or with an oxaziridine to introduce a hydroxyl group.[9-10] This chemistry has been applied to the construction of cyclic β-amino acid motifs and other synthetic targets.[3, 6, 11] In the course of a molecular design project in this lab, we desired products related to **3** but with a heteroatom substituent (Y ≠ H) at the



Scheme 1. Asymmetric Conjugate Addition/Cyclization Method of Davies et al.

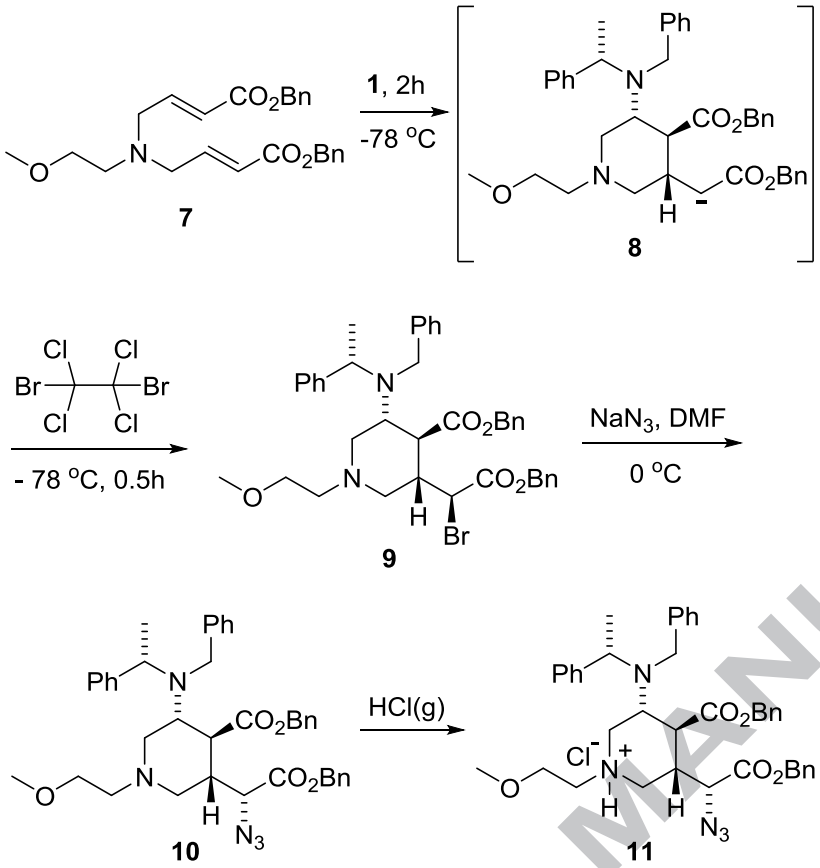


Scheme 2. Conjugate Addition/Cyclization/Aldol Method of Ozeki et al.

position of the cyclization-derived enolate. We report here the diastereoselective trapping of the enolate from conjugate addition/cyclization with a brominating agent and subsequent transformations and structural analysis of the resulting product.

Results and Discussion

The reactant **7** was prepared by bis-alkylation of 2-methoxyethylamine with the known benzyl-4-bromocrotonate[12-13] following procedures for the synthesis of related structures.[3] Reaction with the α–methylbenzylamine-derived lithium amide **1** followed by mild acid quench gave a product **3** (Scheme 1). Efforts were then made to replace the acid quench with a source of electrophilic bromine. Initial attempts using N-bromosuccinimide were unsuccessful, giving a mixture of products. 1,2-dibromotetrachloroethane has been reported as a reagent for the bromination of an organocuprate[14] and for α-bromination of ketones via an enolate intermediate.[15-16] Trapping of the enolate **8** with this reagent gave the desired brominated product **9**, with the major isomer isolated in 79% yield (scheme 3). If bromination occurs from the same relative face as in the trapping with an aldehyde (scheme 2)[7] or Michael acceptor,[8] the major product should have the stereochemistry shown in **9**. The product **9** showed substantial decomposition within 24 h at room temp but was stable for weeks at -20 °C. Reaction of **9** with sodium azide gave the azide product **10**, which was sufficiently stable for further manipulation and analysis.



Scheme 3. Conjugate Addition/Cyclization/Bromination and Conversion to a Crystalline Derivative.

Applying HCl gas to a solution of **10** in ether formed the hydrochloride salt **11** as a solid. **11** was recrystallized from acetonitrile, and a single crystal was selected for analysis. The structure of **11** was obtained via single crystal diffraction. The structure confirmed the expected stereochemistry (Figure 1), with stereocenters formed in the conjugate addition and cyclization having the

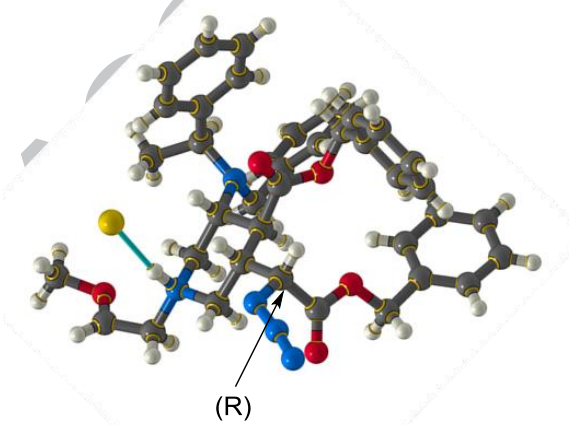
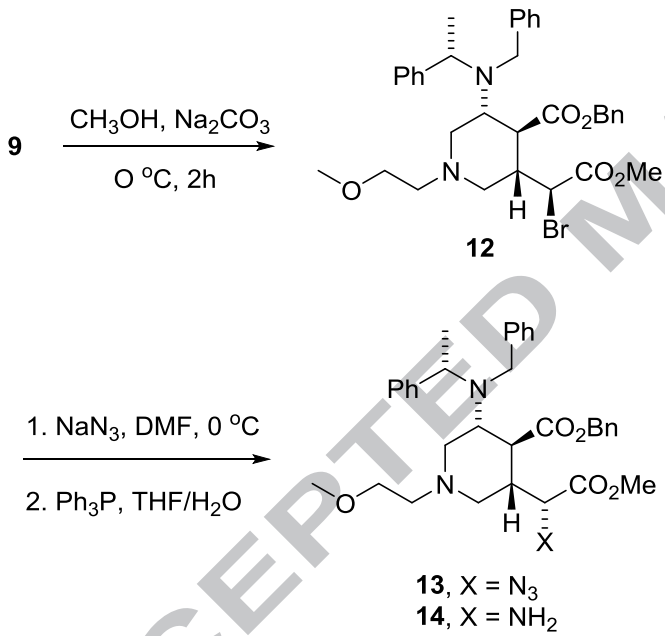


Fig. 1. X-ray crystal structure of 11.

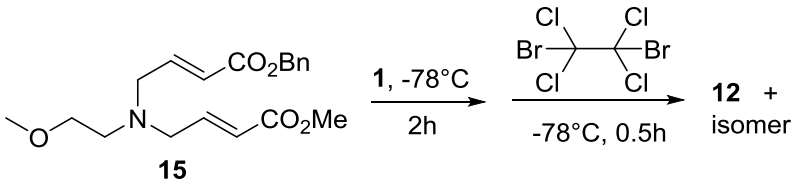
configuration observed in previous studies and the azide bearing carbon having the *R* configuration, consistent with the assigned S configuration in the initial brominated product **9**.

Synthetic targets in this lab require selective manipulation of the two benzyl ester groups. Treatment of the brominated product **9** with sodium carbonate in methanol at 0 °C resulted in selective transesterification of one of the two benzyl esters to form a single benzyl/methyl ester product (scheme 4).[17] The selectivity is attributed to greater reactivity of the α-bromoester due to the inductive effect of bromine to give the product **12** shown, though this is also consistent with selectivity observed in hydrolysis of a pent-3-yl diester of the acid quench product **3** with LiOH.[18] Under the given conditions, no epimerization was detected in the formation of **12** as indicated by a single isomer in the ^{1}H-NMR spectrum. Reaction of **12** with sodium azide gave the azide product **13**, which was subsequently reduced to the amine **14**. Any of a number of methods for cleavage of benzyl esters may permit subsequent selective deprotection of the benzyl ester.[19]



Scheme 4. Selective Transesterification and Subsequent Transformation to an Amine.

Further experiments were conducted to support the assigned regioselectivity in the transesterification step. The nonbrominated product **3** (scheme 1, Y=H) resulting from mild acid quench of the enolate intermediate **8** was subjected to the precise conditions of the transesterification step in forming **12**. No reaction was observed, indicating that the inductive effect of the bromine is necessary for transesterification under these mildly basic conditions and supporting the assigned regioselectivity. When the mixed methyl/benzyl ester **15** was subjected to the cyclization-bromination conditions, it resulted in an approximately 1:1 mixture of **12** and the apparent isomer resulting from initial addition to the β-carbon of the methyl ester rather than the benzyl ester (scheme 5). This was as expected, though 3:1 selectivity for conjugate addition



Scheme 5. Conjugate Addition/Cyclization/Bromination of a Mixed Methyl Benzyl Diester.

to the methyl ester of a mixed methyl, t-butyl ester as well as selective conjugate addition to the ester of a mixed ester/acid have been observed, where 2D NMR experiments were used for structural assignment of the resulting isomers.[20-21] The two products could not be separated but gave two distinct sets of peaks in the ^{1}H-NMR spectrum of the mixture. One set of peaks was identical to those of the product **12** of the transesterification reaction in scheme 4, while the peaks assigned to the isomer were not detected in the transesterification product of **9**. This further supports the formation of the single product **12** in the transesterification reaction.

Efforts are currently underway to use the product **12** from the cyclization/bromination and transesterification sequence in the synthesis of more advanced molecular design targets.

Conclusion

Using a cascade reaction of a tandem conjugate addition/cyclization reaction followed by an in situ bromination, four stereogenic centers were successfully generated in one step. The resulting α–bromoester had a much higher reactivity than the non-brominated ester, enabling selective ester manipulation in the cyclized product.

Acknowledgements

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Supplementary data

Supplementary data (synthetic procedures, compound characterization data, and NMR spectra) associated with this article can be found, in the online version**.** Crystallographic data (excluding structure factors) for compound **11** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1580971. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.Uk).

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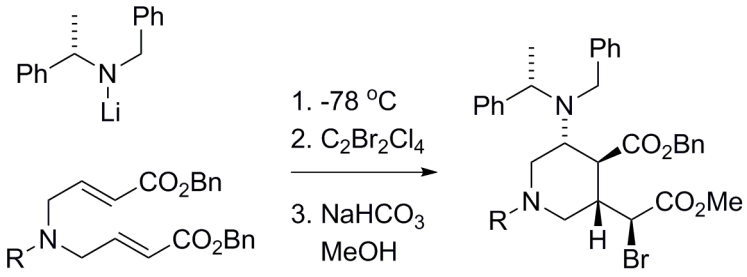

An enolate was quenched stereoselectively with a bromine source.

A highly functionalized piperidine was prepared with four stereocenters.

The structure and stereochemistry was proven by x-ray analysis.

One of two ester groups of the product was modified selectively.