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Base-determinant chemodivergent transformations of chiral 2,3-dibromopropanamide derivative

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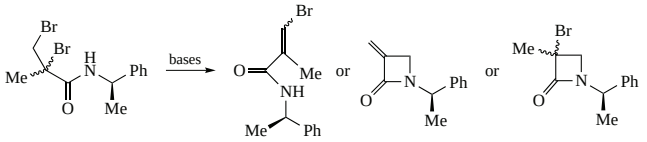
Depending on the base used, reactions of 2,3-dibromo-2-methyl-*N*-[(1*R*)-1-phenylethyl]propanamide with DBU, Bu^{t}OK and NaH in THF lead to β-bromomethacryloylamides, α-methylidene-β-lactam and azetidin-2-ones, respectively.



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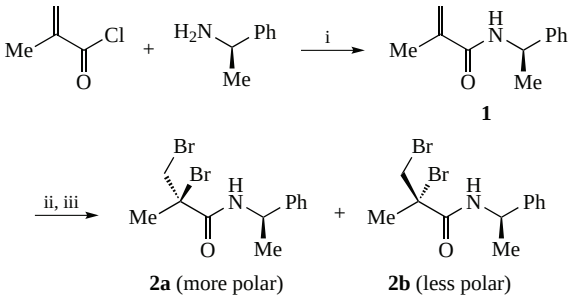
Monocyclic β-lactams represent the ring part of antibacterial monobactam and sulbactam,[1] an Ezetimibe cholesterol absorption inhibitor,[2] azetidinones for carbapenems,[3,4] β-lactam synthons for incorporation of Taxol β-amino ester fragment into the aglycone structure,[5,6] serve as potential models in the study of drug resistance of β-lactams.[7] α-Methylidene-β-lactams (αMβLs) can undergo the Michael reactions, electrophilic addition and lactam ring opening. A number of methods for synthesizing αMβLs have been published, including a synthesis of those containing CF_3 at C^3 by methylenation of the corresponding 3-oxo derivatives,[8] a synthesis employing Pd-catalyzed oxidative carbonylation of *N*-allylamines,[9] approaches to densely functionalized αMβLs from nitrodiene structures,[10] asymmetric allylic amination of Baylis–Hillman adducts with amines followed by cyclization,[11] PPh_3-catalyzed Umpolung cyclization of propylamides.[12]

In the present study, we attempted to construct methylidene-β-lactam moiety by dehydrobrominative cyclization of 2,3-dibromo-2-methylpropanamide derivatives which, in turn, can be prepared by bromination of methacrylamides. Dehydrobromination of 2,3-dibromo-2-methylpropanamides can also afford bromoalkene-type products which were used in the Heck cross-coupling,[13] the Nozaki–Hiyama–Kishi aldol condensation,[14] and for generation of vinyl radicals. We supposed that the choice of proper base and reaction conditions would drive the reaction towards the cyclization route involving amide nitrogen atom.

In our experiments, amide **1** obtained from commercially available methacryloyl chloride and (*R*)-(+)-α-methylbenzylamine was brominated to give a diastereomeric mixture of dibromo derivatives **2** (Scheme 1). Though analytical samples of diastereomers **2a**,**b** were isolated by column chromatography on SiO_2 and the structure of (*S*,*R*)-**2b** was confirmed by XRD (Figure 1),† a more accessible diastereomeric mixture of **2a**,**b** was used in the subsequent reactions.



Scheme 1 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, 0 → 20 °C, 4 h, 83%; ii, Br_2, CH_2Cl_2, room temperature, 1 h, 73%; iii, SiO_2, column chromatography.

Compounds **2a**,**b** are of interest primarily for possible base-promoted intramolecular cyclization reactions. Reaction of dibromide **2** with DBU gives a mixture of dehydrobromination products **3a** and **3b** in a 2 : 1 ratio (Scheme 2). The vinyl proton signal is characteristic in the assignment of isomeric vinyl bromides **3a** and **3b**. For isomer **3a**, it is shifted

† *Crystal data for* **2b**. $C_{12}H_{15}Br_2NO$ (M = 349.05), monoclinic, space group $P2_1$, a = 9.9212(5), b = 16.9866(10) and c = 16.8457(10) Å, β = 100.250(5)°, V = 2793.7(3) Å^3, Z = 8, T = 293(2) K, μ(MoKα) = 5.784 mm^{-1}, d_{calc} = 1.660 g cm^{-3}, F(000) = 1376.0, S = 0.842. Refinement was converged with R_1 = 0.0542, wR_2 = 0.0681 [9526 reflections with $I > 2\sigma(I)$] and R_1 = 0.1819, wR_2 = 0.1055 for all data (13857 reflections). The X-ray diffraction measurements were performed on an Agilent XCalibur (Eos, Gemini) automated four-circle diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å, ω-scan mode, $2\theta_{max}$ = 62°) at ambient temperature (293–298 K). The collected data were processed using the CrysAlisPro program.[15] The structures were solved by direct methods and refined by the full-matrix least-squares method in the anisotropic approximation for non-hydrogen atoms. All hydrogen atoms were generated using the proper HFIX command and refined isotropically using the riding model. The structure was solved with the ShelXT[16] structure solution program using Intrinsic Phasing and refined with the ShelXL[17] refinement package using Least Squares minimisation.

CCDC 1972715 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

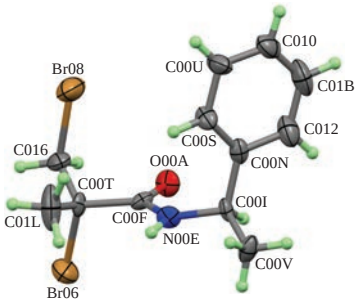
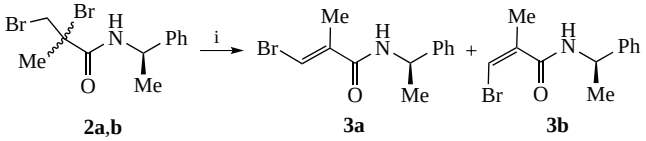


Figure 1 Molecular structure of dibromide (*S*,*R*)-**2b**. Non-hydrogen atoms are represented by thermal vibration ellipsoids (*p* = 30%).

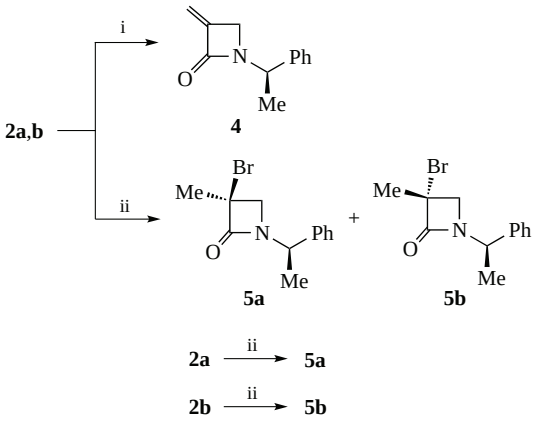


2a,**b** **3a** **3b**

Scheme 2 *Reagents and conditions*: i, DBU, PhH, room temperature, 2 h.

downfield since this proton is located in the carbonyl anisotropy cone.

Treatment of both isomers **2a**,**b** with Bu^{t}OK in THF causes double dehydrobromination leading to α-methylidene-β-lactam **4** (Scheme 3). In case of sodium hydride, bromo β-lactam diastereomers **5a**,**b** are formed in approximately equal amounts. The configuration at a lactam carbon atoms in compounds **5a**,**b** retains in the course of cyclization, which is confirmed by the conversion of individual **2a** and **2b** into **5a** and **5b**, respectively (see Scheme 3, note *R*–*S* switching on displacement of bromine atom).



Scheme 3 *Reagents and conditions*: i, Bu^{t}OK, THF, room temperature, 6 h, 73%; ii, NaH, THF, room temperature, 2 h.

In summary, we described a short and chemo-rational way for synthesizing the aforementioned β-lactams, an α-methylidene-β-lactam and β-bromomethacryloylamides based on common diastereomeric (2*RS*)-2,3-dibromo-2-methyl-*N*-[(1*R*)-1-phenylethyl]propanamides prepared from commercially available methacryloyl chloride and (*R*)-(+)-α-methylbenzylamine. It is also obvious that the approach is versatile in terms of synthesizing various N-substituted derivatives using any primary amine instead of α-methylbenzylamine in the reaction cycle.

This work was performed using the equipment of the Khimiya Center for Collective Use of the Ufa Institute of Chemistry, Russian Academy of Sciences. X-ray diffraction data were obtained using the equipment in Agidel Regional Center for Collective Use at the Ufa Federal Research Centre of RAS. This work was carried out within the subject AAAA-A20-120012090021-4 of the state assignment and with financial support from the Russian Science Foundation (project no. 15-13-00039-P).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.017.

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