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Racemic novel buffer-mediated rearrangement

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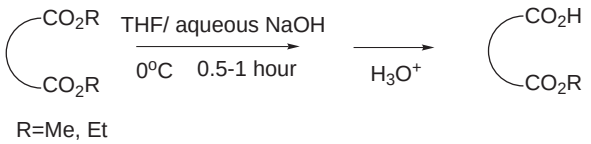
Abstract

A simple application of the highly efficient semi-two-phase monohydrolysis of *meso* diesters is described. Using this reaction, symmetric dialkyl 5,6-epoxybicyclo[2.2.1]hept-2-ene-2,3-dicarboxylates yield 6-formyl-1-alkoxycarbonylbicyclo[3.1.0]hex-2-ene-2-carboxylic acids in a racemic manner in high yields in only two steps, providing additional support for the mechanisms of the semi-two-phase monohydrolysis and the rearrangement.

Keywords: rearrangement; bicyclic aliphatic compound; hydrolysis.

Desymmetrization of *meso* diesters yielding half-esters is a versatile concept for the development of synthetic methodologies for a variety of compounds. Enzymatic desymmetrization of *meso* diesters is one of the most common ways to accomplish this task, although enzymes provide no basis for prediction of reactivities for chemical yields and optical purities. In cases where desymmetrization is to be accomplished in a non-asymmetric manner, usual alkali hydrolysis tends to yield complex mixtures of half-esters, dicarboxylic acids, and starting diesters.

However, recently Niwayama reported a new highly selective monohydrolysis of a series of symmetric diesters using THF and aqueous NaOH solution at 0°C.[1] As opposed to classical alkaline hydrolysis or saponification, this semi-two-phase reaction is quite clean and affords the corresponding half-esters in near-quantitative to modestly high yields for a series of *meso* diesters (Scheme 1).



Scheme 1.

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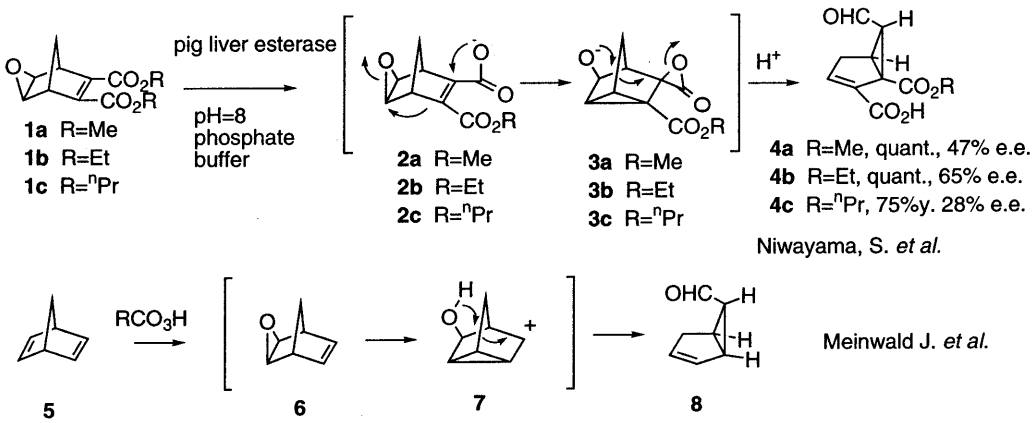
One of the most advantageous features of this reaction is that it can retain labile functional groups intact, presumably because a large portion of the molecule is protected in the THF-enriched medium, which indicates its synthetic versatility.[2] Here one simple application of this semi-two-phase monohydrolysis reaction is described.

Earlier, we reported a novel stereo- and regiospecific chemicoenzymatic rearrangement initiated by enzymatic asymmetric desymmetrization of symmetric diesters, **1a–c**, producing uniquely strained multifunctional compounds, 6-formyl-1-alkoxycarbonylbicyclo[3.1.0]hex-2-ene-2-carboxylic acids, **4a–c** (Scheme 2).[3] The rearranged products have the same core structure, bicyclo[3.1.0]hex-2-ene-*endo*-carboaldehyde, **8**, reported by Meinwald et al. (Scheme 2).[4] This skeleton has been known to be a useful synthetic building block that forms bioactive molecules such as nucleoside analogues[5] or reactive species for further skeletal conversions.[6] However, the completely unpredictable enzymatic monohydrolysis obstructed further synthetic development of the rearranged products, **4a–c**.

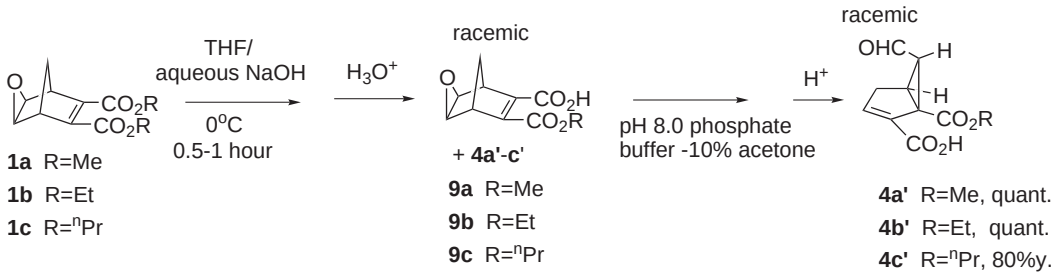


Scheme 2.

Here a non-enzymatic method is presented for preparation of the rearranged product, **4**, in high yields using the semi-two-phase selective monohydrolysis reaction.

The semi-two-phase monohydrolysis reaction afforded half esters **9a–c** in high to near-quantitative yields containing only trace to small amounts of the rearranged products, **4a′–c′**, starting from the corresponding symmetric dimethyl, diethyl and di-*n*-propyl diesters, **1a–c**. As noted earlier, the epoxy groups stayed mostly intact without being transformed into the corresponding diols, except for **1c** which was accompanied by a small amount of by-product, which is presumably mainly a small amount of the corresponding diol and the rearranged product. In fact, the minimum amount of the 0.25N NaOH solution required for completing the monohydrolysis of di-*n*-propylester **1c**, was approximately five times the equivalent required for monohydrolysis of dimethylester **1a**, while diethylester **1b** needed only approximately three times the equivalent required for monohydrolysis of dimethylester **1a**.

Upon dissolving **9a–c** in a slightly basic (pH 8) phosphate buffer solution containing 10% acetone, which is the same buffer medium as for the pig liver esterase monoydrolysis, at room temperature overnight, the rearranged products **4a′**, **4b′** and **4c′** were obtained in racemic forms in high yields after routine silica gel column chromatography (Scheme 3).[7]



Scheme 3.

This rearrangement not only enables production of the rearranged products in a non-enzymatic manner, but also provides additional support for the mechanism of the chemicoenzymatic rearrangement as well as the semi-two-phase monohydrolysis of diesters. Namely, the enzymes merely desymmetrize the diesters, and the resultant carboxylate anions undergo this rearrangement facilitated by the protic buffer medium. We recently confirmed the structure of the rearranged products of the acetal derivative of **4a**′ in a racemic form by X-ray crystal analysis.[3d]

During the monohydrolysis, it is expected that a large portion of each of the diesters is covered by the aprotic solvent, the THF-enriched medium, while carboalkoxy groups, the most hydrophilic functional groups, are likely to point toward the interface between the THF and aqueous phases and that the hydrolysis occurs at the interface. This observation, that all of the diesters underwent the monohydrolysis without being accompanied by a large amount of the rearranged products, supports the hypothesis that the monohydrolysis is primarily occurring at the interface between the aqueous phase and the organic phase. This is also consistent with our earlier observation that the carboxylate anion of **2a** generated by *n*-BuLi in THF with no buffer medium does not undergo this rearrangement.[3a] In addition, the hydrophobicity of the carboalkoxy group increases in the order of COOMe<COOEt<COO^{n}Pr, therefore, the increased amount of the NaOH solution required to complete the monohydrolysis in the semi-two-phase medium in this order is also consistent with this hypothesis.

In conclusion, a straightforward method for production of the multifunctional bicyclo[3.1.0]hex-2-ene system has been established by desymmetrization of *meso* diesters, which can easily be obtained from inexpensive sources, applying the semi-two-phase monohydrolysis reaction in only two steps in high yields. Further synthetic expansions of the scope of this hydrolysis and rearrangement are under investigation.

Acknowledgements

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7. Spectrum data for **4a**′–**c**′are as follows. **4a**′: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.39 (1H, d, $J=3.6$), 6.8 (1H, m), 3.77 (3H, s), 2.9 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 169.6, 167.6, 147.1, 131.8. 52.7, 44.5, 34.8, 34.7, 33.4. IR (neat, cm^{-1}) 2550–3000, 1735, 1720, 1710, 1266; HRMS calcd for $C_{10}H_{10}O_5$: 210.0528, found 210.0534. **4b**′: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.36 (1H, d, $J=3.9$), 6.8 (1H, m), 4.25 (1H, dq, $J=10.8$, 7.2), 4.13 (1H, dq, $J=10.8$, 7.2), 2.9 (3H, m), 2.6 (1H, m), 1.23 (3H, t, $J=7.2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 169.1, 168.1, 146.9, 132.0, 61.8, 44.7, 34.8, 34.6, 33.4, 14.0. IR (neat, cm^{-1}) 2500–3000, 1732, 1722, 1710, 1264; HRMS calcd for $C_{11}H_{12}O_5$: 224.0685, found 224.0686. **4c**′: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.39 (1H, d, $J=3.9$), 6.9 (1H, m), 4.19 (1H, dt, $J=10.8$, 7.2), 4.05 (1H, dt, $J=10.8$, 7.2), 2.9 (3H, m), 2.6 (1H, m), 1.66 (2H, sextet, $J=7.2$), 0.93 (3H, t, $J=7.2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0, 169.2, 168.5, 146.8, 132.0, 67.4, 44.7, 34.8, 34.7, 33.4, 21.8, 10.3. IR (neat, cm^{-1}) 2600–3000, 1735, 1719, 1710, 1255; HRMS calcd for $C_{12}H_{14}O_5$: 238.0842, found 238.0845.