Stereoselective Synthesis

A Tandem Semipinacol Rearrangement/Alkylation of α-Epoxy Alcohols: An Efficient and Stereoselective Approach to Multifunctional 1,3-Diols**

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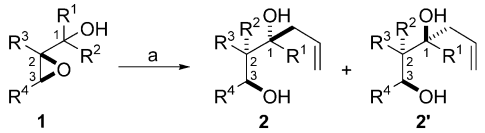
Multifunctional 1,3-diols with an allyl or a propargyl group and three consecutive stereocenters, two of which are quaternary carbon atoms, form a class of important building blocks that is required for the synthesis of many biologically significant molecules, such as sieboldine A,[1] furaquinocins,[2] and ingenol.[3] The stereoselective construction of the quaternary carbon centers, in particular, has received considerable attention .[4] However, efficient construction of adjacent multiple stereocenters with two quaternary carbon atoms is still a challenging area of study.[5] During the past several years, our studies on tandem reactions of α-heterocyclopropane alcohols have resulted in the stereoselective construction of 2-quaternary 1,3-diheteroatom units by tandem rearrangement/reduction reactions of α-heterocyclopropane alcohols.[6] However, the tandem rearrangement/alkylation reactions of these alcohols, which would present an approach to the construction of more synthetically important and versatile 1,3-diheteroatom units, has not been accessed to date. Recently, we successfully developed a novel tandem reaction of α-epoxy alcohols with $RB(OH)_2$ (R = allyl and allenyl). The synthetically important features of this sequence include the following: 1) smooth completion of the two different chemical transformations—the stereospecific boron-promoted semipinacol rearrangement of the α-epoxy alcohol and the subsequent allylation or propargylation of the intermediate β-hydroxy ketone; 2) diastereoselective construction of the three consecutive stereogenic centers, two of which are quaternary, with one allyl or propargyl group; 3) pivotal dual roles of $RB(OH)_2$: lewis acidity and alkylating ability; it is generally assumed to act as an alkylating reagent,[7] and to our knowledge, no report on the dual nature of the $RB(OH)_2$ has been published previously; 4) the relative stereochemistry of C1 in the 1,3-diol product **2**/**2′**, which is independent of the relative configuration of C1 in the substrate **1**, can be tuned by the substituent R^4 on **1**. Consequently, this tandem transformation would offer extensive application in organic synthesis. Herein, we present the results of our investigation and its synthetic application.

We initially studied the tandem reaction of α-epoxy alcohols with allylboronic acid ($RB(OH)_2$, R = allyl). The α-epoxy alcohol substrates **1** were prepared in racemic forms by epoxidation of the corresponding allylic alcohols with *m*-chloroperbenzoic acid (*m*CPBA) or $tBuO_2H/[VO(acac)_2]$ (acac = acetylacetonoate) according to literature procedures.[8] A solution of the substrate **1** (1.0 equiv) and the freshly prepared allylboronic acid[9] (1.2 equiv) in $Cl(CH_2)_2Cl$ was stirred at ambient temperature in an argon atmosphere for 6–18 h, during which time a diastereoselective tandem semipinacol rearrangement/allylation proceeded smoothly to generate the 1-allyl-1,3-diols **2** and/or **2′** in good yields (Scheme 1). Solvent effects were also observed in this reaction. For example, the reaction proceeded readily in



Scheme 1. The tandem semipinacol rearrangement/allylation of α-epoxy alcohols **1**. a) allylboronic acid, $Cl(CH_2)_2Cl$, room temperature (RT).

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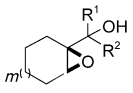
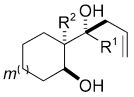
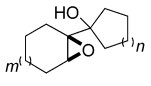
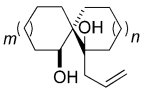
$Cl(CH_2)_2Cl$, CH_2Cl_2, or toluene, but slowed down in Et_2O, and could not even be initiated in protic solvents such as EtOH.

As shown in Table 1, various substrates proved to be suitable for this procedure; the migrating group R^2 could be

Table 1: Tandem semipinacol rearrangement/allylation of α-epoxy alcohols **1** with allylboronic acid.

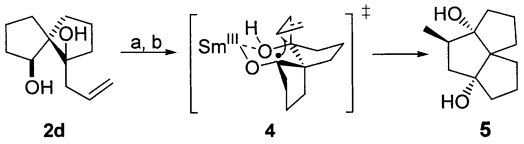
Entry	Substrate	Erythro:threo[a]	Major product	**2**:**2′**[b]	Yield [%][c]
					
1	**1a**: $m=1$, $R^1=Me$, $R^2=Ph$	70:30	**2a**	>99:<1	75
2	**1b**: $m=0$, R^1, $R^2=Ph$		**2b**	>99:<1	81
3	**1c**: $m=0$, $R^1=Me$, $R^2=2$-thienyl	88:12	**2c**	>99:<1	69
					
4	**1d**: $m=0$, $n=0$		**2d**	71:29	>99
5	**1e**: $m=1$, $n=0$		**2e**	85:15	80
6	**1f**: $m=1$, $n=1$		**2f**	>99:<1	91
					
7	**1g**: $R^1=Me$, $R^2=$cyclopropyl	78:22	**2g′**	31:69	71
8	**1h**: $R^1=Me$, $R^2=Ph$	69:31	**2h′**	<1:>99	61

[a] The ratio of two C1 epimers in substrate **1**; see ref. [8]. [b] The ratios were determined by ^1H NMR spectroscopy. [c] Yield of the isolated product.

aryl or alkyl, thus demonstrating its broad scope of application. ^1H NMR NOE experiments on the acetonide of the 1,3-diols **2a** indicated that when R^3 and R^4 formed a linker or R^4 was an alkyl group (entries 1–6), the two adjacent stereocenters C2 and C3 had a *trans* relative configuration (namely, C2–R^2 was *trans* to C3–OH) and the C1–OH group had predominantly the α configuration.[10] This stereochemistry was derived from the highly stereospecific boron-promoted semipinacol rearrangement as well as the subsequent diastereoselective intramolecular allylation. Notably, a mixture of two C1 epimers in the substrates **1** (entries 1, 3, 7, and 8), such as is present in **1a** and **1c**, generated one diastereoisomeric product **2a** and **2c**, respectively, which indicated that the migration of R^2 from C1 to C2 was highly stereoselective irrespective of the relative configuration of C1 in **1**. In the spirocyclic systems examined (entries 4–6 of Table 1), *cis*,-*trans*-spirocyclo-1,3-diols **2d**–**2f** were obtained as the major products, whose relative configuration was further determined unambiguously by the X-ray crystallographic analysis of **2f**.[11] The relative stereochemistry of the minor products was determined by ^1H NMR NOE experiments of the benzylidene acetal of **2d′**.[10]

When the substrate possessed nonlinked R^3 and R^4 groups, and R^4 was hydrogen, an interesting inversion of the configuration was found on C1–OH. For example in entries 7 and 8, the major product **2′** was obtained in good yield with a C1–OH group in a β configuration.[10] It is notable that for entry 8, when the migrating group R^2 was the favorable Ph group, the completely reversed C1 stereochemistry of **2h′** was observed. This tunable stereoselectivity arising from the structure of the substrate, to our knowledge, was first observed in the tandem reactions of α-epoxy alcohols. We also found that the nature of the migrating group R^2 in the substrates had a significant influence on this tandem reaction. For example, when R^2 was *n*-butyl (*n*Bu) or benzyl (Bn), the expected rearrangement/allylation could not readily take place.

The above-mentioned multifunctional 1,3-diols may be the key building blocks for the synthesis of some significant bioactive terpenic natural products with polycyclic rings and polyquaternary centers, such as pentalenene,[12] 5-oxosilphiperfol-6-ene,[13] subergorgic acid,[14] isocomene,[15] crinipelline A,[16] and others, which are still attracting considerable attention from synthetic chemists. As an example here, we have constructed the unusual tricyclo[6.3.0.0] structural motif **5** from the multifunctional 1,3-diol **2d** (Scheme 2) in an overall yield of 50% by just two steps (PDC oxidation and the stereocontrolled cyclization under SmI_2)[17] wherein the diastereoselectivity demonstrated was in accordance with the transition state **4** from the previously proposed mechanism for the SmI_2-mediated cyclization.[17a] This tricyclic skeleton **5** would act as the key and general intermediate for the synthesis of the above natural products if suitable substrates were used.



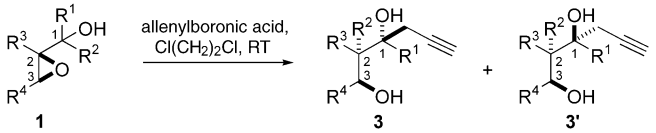
2d **4** **5**

Scheme 2. Synthesis of **5**. a) PDC, CH_2Cl_2 and b) SmI_2, HMPA, *t*BuOH, THF, 50% over two steps. PDC = pyridinium dichromate.

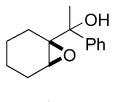
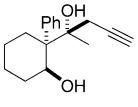
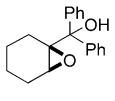
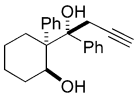
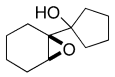
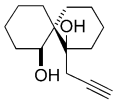
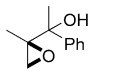
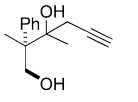
To further expand the scope of this tandem reaction we considered the use of the more versatile propargylic systems.[18] Further investigation was, therefore, aimed at the tandem reaction of α-epoxy alcohols with allenylboronic acid ($RB(OH)_2$, R = allenyl),[19] and the cyclic substrates (**1a**, **1f**,, and **1k** R^4 = alkyl) and the acyclic one (**1h**, $R^4=H$) were subjected to the reaction sequence. The 1-progargyl-2-quaternary-1,3-diols were obtained in moderate yields. From Table 2 (entries 1–3) it can be seen that the diastereoselectivity exhibited in the construction of the three adjacent stereocenters in this reaction is the same as that of entries 1–6 in Table 1, which was further confirmed by ^1H NMR NOE experiments of the acetonide of **3a**.[10] Partial reversion of the C1 stereochemistry was also observed (entry 4 of Table 2).

On the basis of the above experimental results and the process of semipinacol rearrangement/alkylation of α-epoxy

Table 2: Tandem reaction of α-epoxy alcohols **1** promoted by allenylboronic acid.



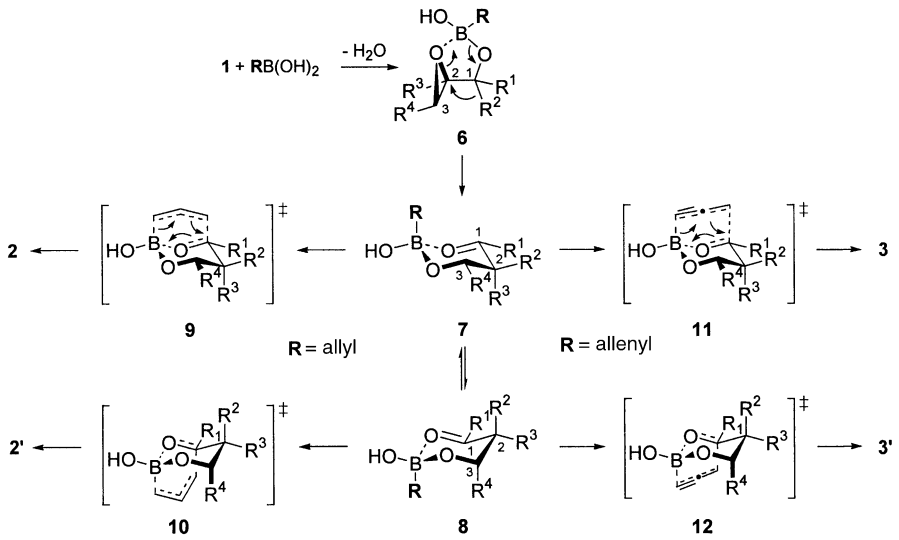
1 **3** **3'**

Entry	Substrate	Erythro:threo[a]	Major product	**3**:**3'**[b]	Yield [%][c]	*T*
1	 **1a**	70:30	 **3a**	>99:<1	55	70 h
2	 **1k**		 **3b**	>99:<1	40	78 h
3	 **1f**		 **3c**	>99:<1	74	65 h
4	 **1h**	69:31	 **3d/3d'**	1:1	48	4 days

[a] The ratio of two C1 epimers in substrate **1**; see ref. [8]. [b] The ratios were determined by ^{1}H NMR spectroscopy. [c] Yield of the isolated product.

alcohols, the mechanism for the generation of the stereochemistry of the three contiguous stereocenters could be explained (Scheme 3). In the first stage, the Lewis acidic boron center readily promoted the semipinacol rearrangement through coordination with the epoxy oxygen atom. Cleavage of the activated C2–O bond of the epoxide then occurred concomitantly with the stereospecific 1,2-migration of R^2 in a transition-state geometry resembling an S_N2 process. In this step, the relative stereochemistry of the C2 and C3 centers in the final 1,3-diol products was perfectly controlled. On the basis of the distinct dependence of the C1 stereochemistry upon the substrate structure, particularly on the nature of R^4 in **1**, the chelated bicyclic transition states **9**/**10** for allylation and **11**/**12** for progargylation were proposed, where **9**/**11** and **10**/**12** resulted from the boron-coordinated β-hydroxy ketones **7** and **8**, respectively. When the substituent R^4 was CH_2, it could be seen that the steric hindrance between the axial alkyl R^4 and the axial allyl or propargyl groups, respectively, clearly existed in **10** and **12**, and the subsequent allylation or progargylation process in this tandem reaction occurred by means of the favorable intermediates **9** or **11** to yield the final 1,3-diol products with C1–OH group with an α configuration (entries 1–6 of Table 1 and entries 1–3 of Table 2). However, when R^4 was hydrogen, the unfavorable steric effect of R^4 did not exist in **10** and **12**, which resulted in the inverse stereochemistry at C1. In the case of entry 7 of Table 1 (R^4 = H, R^2 = cyclopropanyl), the bulky R^2 group was *cis* to the allyl group in the transition state **9**, and diols **2g′** was obtained as the major product with a C1–OH group with a β configuration via the more favorable transition state **10**. Complete inversion of the C1 stereochemistry was observed in entry 8 of Table 1 (R^4 = H, R^2 = Ph), possibly not only because of the favorable *anti* configuration between the bulky R^2 (R^2 = Ph) and allyl groups in **10**, but also because of the preferred conformation of the axial phenyl group.[20]

In conclusion, we have successfully developed a novel tandem semipinacol rearrangement/alkylation of α-epoxy alcohols. This reaction has proved to be a general, efficient and short method for construction of multifunctional 1,3-diols with three adjacent stereocenters, two of which are quaternary carbon atoms. We believe that this tandem reaction will find extensive application in the synthesis of important complex organic compounds, especially those with polycycles and multiple stereocenters.



Scheme 3. Proposed mechanism of the tandem semipinacol rearrangement/alkylation reaction of α-epoxy alcohols.

Experimental Section

General procedure for the tandem reaction of α-epoxy alcohol with allylboronic acid or allenylboronic acid (Table 1, entry 1): A solution of allylboronic acid (103.2 mg, 1.2 mmol) in dry 1,2-dichloroethane (20 mL) was added to a solution of **1a** (218 mg, 1 mmol) in dry 1,2-dichloroethane (20 mL) at room temperature in an argon atmosphere. The reaction mixture was stirred at room temperature to ensure completion of the reac-

tion. The 1,2-dichloroethane was removed under reduced pressure and the residue dissolved in diethyl ether (30 mL) before oxidizing with NaOH(2N)/H_2O_2(30%). The aqueous layer was added to saturated brine (20 mL) and then extracted with ethyl acetate (5 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the crude product by column chromatography on silica gel (petroleum/ethyl acetate 35/1→15/1) afforded **2a**/**2a**′ (195 mg, 0.75 mmol, 75%).

5: A solution of **2d** (100 mg, 0.5 mmol) in dichloromethane was mixed with a solution of pyridinium dichromate (207 mg, 1.1 mmol) in dichloromethane with stirring at room temperature. Reaction was completed in 1 h and quenched with Et_2O. The mixture was filtered quickly through a short column of basic Al_2O_3, washed with saturated brine, and dried over anhydrous Na_2SO_4. The product was labile to column chromatography, so the 5-exo-cyclization was performed directly on the crude product by using literature procedures.[17a] The solvent was removed under reduced pressure. A solution of the residue and *t*BuOH (741 mg, 1 mmol) in tetrahydrofuran (THF) (20 mL) was added dropwise to the deep purple solution of SmI_2[21] (0.1M in THF, 15 mL, 1.5 mmol) and hexamethylphosphoramide (HMPA; 1.97 g, 11 mmol) in THF. Reaction was completed in 10 min and was quenched with saturated $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the crude product by column chromatography on silica gel (petroleum/ethyl acetate 35/1) afforded **5** (49 mg, 0.25 mmol, 50% over two steps).

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[11] CCDC-223949 (**2f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge by accessing www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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