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Tetrahedron Letters 45 (2004) 9123–9126
Tetrahedron Letters

A stereoselective synthesis of silylated epoxycyclopentanols bearing four contiguous stereogenic centers

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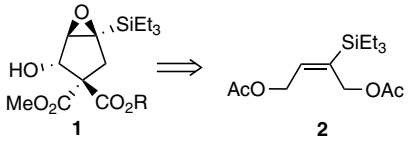
Received 6 July 2004; revised 1 October 2004; accepted 4 October 2004

Abstract—A palladium-catalyzed Tsuji–Trost alkylation of (*E*)-2-triethylsilyl-1,4-diacetoxy-but-2-ene with *tert*-butyl methyl malonate has been performed in excellent chemo and stereoselectivities. The allylated product has been further transformed in few steps in silylated epoxycyclopentanols bearing four controlled stereogenic carbons. The key reaction is a mild tandem oxidation–aldolization induced by DMP or IBX reagents.

In earlier work, dealing with the reactivity of silylated vinyl epoxides, we prepared various enantiomerically pure silylated epoxyalcohols, which are good precursors of vinyl epoxides with well-defined reactivities. For example, in the presence of palladium catalyst, we observed stereoselective silicon 1,2-shift,[1] which allowed the obtention of various α-silylated-β,γ-unsaturated aldehydes.[2] These compounds were further used to prepare highly functionalized lactones.[3] On the other hand, during the preparation of *cis* silylated vinyloxiranes bearing a malonate function, we described an original in situ oxidation–aldolization[4] of some of the epoxyalcohol precursors.[5] This stereoselective cyclization allowed the enantioselective preparation of cyclopentanols with three contiguous stereogenic carbons.[6] We anticipated that replacing the dimethyl malonate function for a prochiral one, where two different electron-withdrawing groups are present, should give an access to more elaborated silylated epoxycyclopentanols with four contiguous stereogenic centers. Such cyclopentanols could be good candidates for the preparation of various C5 polyhydroxylated carbocycles[7] such as carbofuranoses[8] as well as carbonucleosides,[9] which have been described to have various biological activities.[10]

We report here the stereoselective preparation of silylated epoxy cyclopentanols[11] of type **1** bearing a mixed methyl and *tert*-butyl malonate function (Scheme 1). Starting from these esters, we also described a direct intramolecular lactonization decarboxylation giving an access to cyclopentene epoxides. The introduction of the mixed malonate function has been performed by a chemoselective Tsuji–Trost palladium-catalyzed alkylation of the already described silylated butene-1,4-diol diacetate **2**.[12] As expected, this reaction gave the mixed malonate derivative **3b** in a 98/2 *E*/*Z* ratio (Scheme 2).[13]

Even if this compound could be isolated in 75% yield after purification, the crude was pure enough to be directly used in the next step.[14] Deprotection of the remaining acetate was performed in methanol in the presence of 20 mol% of K_2CO_3 giving **4b** in 65% yield over three steps from the commercially available 1,4-butyne diol diacetate. It should be noted here that anhydrous methanol was crucial in this last step to observe reproducible results as well as complete conversion of the starting material. Indeed, in a control experiment,



Scheme 1. Preparation of silylated cyclopentanols.

Keywords: Oxidation; Aldolization; Cyclopentanols; Silicon derivatives.
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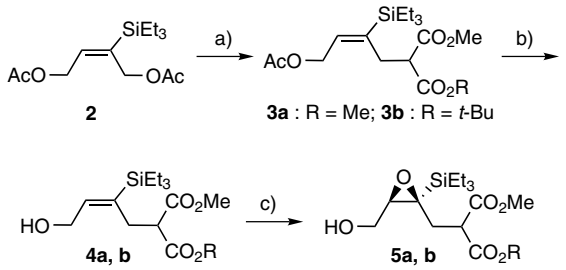
doi:10.1016/j.tetlet.2004.10.017



Scheme 2. Reagents and conditions. (a) $Pd(OAc)_2$ (0.5 mol%), dppe (1 mol%), sodium malonate (1.1 equiv), THF 0 °C 2 h then rt overnight; (**3a**: 85%; **3b**: 75%). (b) K_2CO_3 (20 mol%), anhydrous MeOH rt 5 h, (**4a**: 81%; **4b**: 65% for three steps). (c) m-CPBA (2 equiv), CH_2Cl_2, rt, 5 h, (**5a**: 86%; **5b**: 70%).

we demonstrated that the presence of the acidic proton onto the malonate function ($pK_a = 15$ in DMSO)[15] was responsible for this behavior.

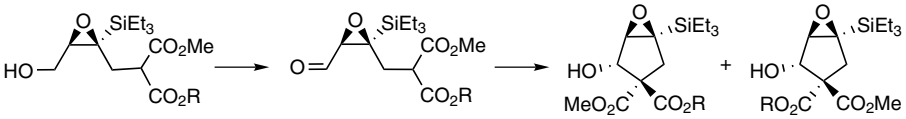
Having in hand the silylated allylic alcohol **4b** we next carried out the epoxidation with m-CPBA (2 equiv) in DCM. At this stage, an inseparable 1/1 mixture of two diastereomers **5b** was obtained, which could be isolated in 70% yield or directly used in the next step.[14]

Some classical methods for oxidation of primary alcohols which have been tested on **5a** gave the expected cyclopentanol **1a** as well as the over oxidized cyclopentanone.[5] The protocol using catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of stoichiometric *N*-methylmorpholine-*N*-oxide (NMO),[16] applied to **6a** provided the cyclopentanol **1a** as the sole product. The same procedure, proved to be less selective for **5b** in large scales. Mixture of cyclopentanol and cyclopentanone were obtained in good yields but in variable ratio. We thus turned our attention toward hypervalent iodide derivatives (Table 1).[17] Dess–Martin periodinane (DMP)[18] and his benziodoxole oxide precursor (2-iodoxybenzoic acid, IBX)[19] are recognized and frequently used as mild oxidizing reagents[20] for the conversion of alcohols to aldehydes or ketones.[21]

We first tested these two oxidizing reagents with the symmetrical malonate alcohol **5a**. In the presence of an equimolar amount of IBX in DMSO, depending on reaction times, we obtained either the corresponding aldehyde **6a** or the cyclopentanol **1a**. Indeed, after 1 h, **6a** could be isolated as the sole product whereas after 2 h, a 75/25 mixture of both **6a** and **1a** was observed on the ^1H NMR of the crude. Finally, total disappearance of **6a** occurred after 5 h at rt giving **1a** in 61% yield after purification (Table 1 entries 1–3). DMP in CH_2Cl_2, which is a smoother oxidizing reagent than IBX, usually gave the aldehyde **6a** in quantitative yield after 2 h (Table 1, entry 4).[22] An in situ basic treatment with Et_3N delivered the corresponding cyclopentanol **1a** in 61% yield (Table 1, entry 5). The *trans* relationship between the two oxygens of the epoxy cyclopentanols of **1a** was based on NMR analysis of 1D and 2D experiments and confirmed by an X-ray structure determination of the corresponding acetate derivative.[23]

The conditions to selectively transform the epoxyalcohol **5a** into the aldehyde **6a** or the cyclopentanol **1a** established, we studied the prochiral mixed malonate derivative **5b**. Reaction of **5b** with IBX, at rt in DMSO, produced a 3/1 mixture of two diastereomeric cyclopentanols **1b** and **1b′** which have been separated by flash chromatography in 49% and 16% yield, respectively (Table 1 entry 6).[24] In order to change the observed diastereoselectivity of the reaction, decrease of the temperature might be required. As it is not possible with IBX in DMSO (mp: 18.4 °C), we first oxidized **5b** into the aldehyde **6b** by the used of the Dess–Martin periodinane in DCM. **6b** was then converted at −20 °C into the corresponding cyclopentanol by the addition of Et_3N. Careful examination of crude mixture by ^1H NMR showed the diastereomeric ratio to be similar to the one observed at rt in DMSO (Table 1, entry 7). We could anticipate that the major stereomer should be **1b** due to the bulkiness of the *tert*-butyl ester function. Unexpectedly, the determination of the relative configuration of the fourth stereogenic center of cyclopentanols **1b** and **1b′** has not been possible by direct analysis of the NMR

Table 1. Preparation of aldehydes **6** and cyclopentanols **1**



Entry	5	Conditions	6 (%)[a]	1 (%)[a]	d.r. (1b/1b′)
1	**a** (R = Me)	IBX, 1 h, rt	100	—	—
2	**a**	IBX, 2 h, rt	75[b]	25[b]	—
3	**a**	IBX, 5 h, rt	—	61	—
4	**a**	DMP, 2 h, rt	98	—	—
5	**a**	DMP, 2 h then Et_3N, 5 h, rt	—	61	—
6	**b** (R = *t*-Bu)	IBX, 5 h, rt	—	65	75/25
7	**b**	DMP, 2 h then Et_3N, 5 h, −20 °C	—	62	75/25

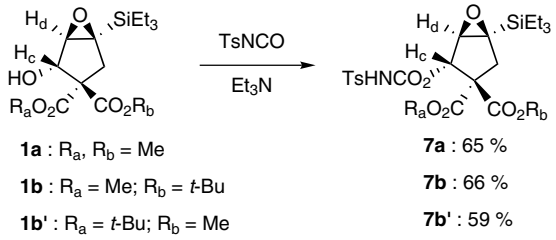
[a] Isolated yields.
[b] **6a/1a** ratio determined by ^1H NMR.

spectra as both compounds presented very similar chemical shifts.

On the other hand, we had observed that **7a**, the *N*-tosyl carbamate derivative of the cyclopentanol **1a**, presented a significative change in the chemical shift of only some characteristic protons (selected chemical shifts are reported in Table 2). As expected, H_c, which is directly connected to the modified alcohol was deshielded by 0.88 ppm, whereas H_d was unexpectedly not influenced. The interesting information came from the fact that the protons of only one of the two methyl ester functions were sensitive to the chemical modification (Table 2, entries 1 and 2).[25] Initially, the two singlets attributed to the methyl esters of **1a** were at 3.76 and 3.74 ppm. After formation of the carbamate function, the *cis* methyl ester protons have been shifted to higher field by 0.24 ppm while the *trans* ones were only slightly modified by −0.03 ppm (Table 2, entry 2).

With these spectral informations in mind, we decided to convert cyclopentanols **1b** and **1b′** into the corresponding *N*-tosyl carbamates. Treatment of each compounds with *N*-tosyl isocyanates in the presence of Et_3N gave the carbamates **7b** and **7b′** in 66% and 59% yields, respectively (Scheme 3). The lower yield observed for **7b′** could be explained by the higher steric hindrance of the secondary alcohol due to the presence of the *cis* *tert*-butyl ester function. As expected, the ^{1}H NMR spectra of the carbamate **7b** showed a difference of −0.16 ppm for the methyl ester signal (δR_a: 3.53 vs 3.70 ppm) whereas no significative shift was observed for the *tert*-butyl protons (Table 2, entries 3 and 4). Finally, for the second diastereomer **6b′** a −0.20 ppm shift was observed for the *tert*-butyl ester function (1.22 vs 1.42 ppm) with no difference for the methyl ester protons (δR_b, entries 5 and 6). In conclusion, these NMR studies allowed us to determine the relative configurations of the two diastereomeric cyclopentanols obtained during the in situ oxidation–aldolization of the acyclic compound **5b**. As it was anticipated, **1b**, the major cyclopentanol, resulted from an approach which minimizes the interaction between the bulky *tert*-butyl ester group and the aldehyde, precursor of the alcohol function.

The described silylated epoxycyclopentanols **1** are highly functionalized compounds, which bear one nucleophilic alcohol (vide supra) and four electrophilic centers. Concerning the epoxy function, the presence of the triethyl silyl group may have two opposite effects. First, it is known that nucleophiles tend to react at the carbon proximate to the silicon atom.[26] Second, triethyl silyl

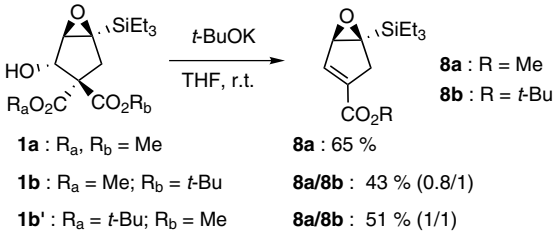


Scheme 3. Preparation of carbamates **7**.

group could participate to the steric hindrance of the α face of the cyclopentanols **1** diminishing the overall reactivity of the epoxy function. We first turned our attention toward an intramolecular reaction, which may be less prone to such steric interactions. We have demonstrated that the alcohol moiety was able to react with electrophiles under slightly basic conditions (vide supra). Moreover, deprotonation of the alcohol function of **1a** with bases such as NaH or *t*-BuOK produced a silylated cyclopentene epoxide **8a** in 65% yield (Scheme 4).[27] This compound results from a lactonization followed by a decarboxylative process[28] due to the high strain of the tricyclic skeleton.[29] Such epoxides could be interesting while some analogues have been described as versatile synthons for the preparation of aristeromycins derivatives with antiviral activity.[30]

Applied to pure **1b** or **1b′**, we had anticipated that, in basic media, retro aldolization could give a fast epimerization to form a mixture of both alkoxides of **1b** and **1b′**. Coupled with a faster lactonization of the methyl ester versus the *tert*-butyl ester one, we expected to displace the equilibrium toward the formation of **8b** as the major alkene.

Surprisingly, with either **1b** or **1b′**, no chemoselectivity was observed. Indeed, in these basic conditions, a 1/1 mixture of the two cyclopentenes **8a** and **8b** was



Scheme 4. Preparation of cyclopentene epoxides **8**.

Table 2. Selected ^{1}H NMR chemical shifts of compounds **1** and **7**

Entry	Compound	δR_a (ppm)	$\Delta\delta R_a$ (ppm)	δR_b (ppm)	$\Delta\delta R_b$ (ppm)	δH_c (ppm)	$\Delta\delta H_c$ (ppm)	δH_d (ppm)	$\Delta\delta H_d$ (ppm)
1	**1a**	3.76 (R_a = Me)		3.74 (R_b = Me)		5.13		3.38	
2	**7a**	3.52 (R_a = Me)	−0.24	3.71 (R_b = Me)	−0.03	6.01	+0.88	3.36	−0.02
3	**1b**	3.70 (R_a = Me)		1.42 (R_b = *t*-Bu)		5.05		3.33	
4	**7b**	3.53 (R_a = Me)	−0.16	1.41 (R_b = *t*-Bu)	−0.01	5.94	+0.89	3.33	0.0
5	**1b′**	1.42 (R_a = *t*-Bu)		3.72 (R_b = Me)		5.04		3.32	
6	**7b′**	1.22 (R_a = *t*-Bu)	−0.20	3.69 (R_b = Me)	−0.03	6.01	+0.97	3.32	0.0

obtained. In this process, the lactonization of the *tert*-butyl ester function[31] occurred at a similar rate as for the methyl ester one.

In conclusion, we have reported a stereoselective preparation of silylated epoxy cyclopentanols. The stereochemistry of two of the four stereogenic centers is controlled during the aldolization by the presence of the epoxysilyl function. Since this one could be introduced by Sharpless asymmetric epoxidation, this reaction could be useful for the preparation of C5 cyclic compounds possessing interesting biological activity.

Acknowledgements

We thank CNRS, Université Pierre et Marie Curie, the Institut Universitaire de France, of which M.M. is a member, for financial support and C. Turpin for technical assistance in the preparation of IBX and DMP.[32]

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