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Highly stereoselective and easy synthesis of enantiopure phosphoranyl oxiranes

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Abstract—The highly stereoselective synthesis of enantiopure phosphoranyl alkyl oxiranes has been accomplished by the addition of a nucleophilic stable phosphino(silyl)carbene to chiral aldehydes prepared from (−)-verbenone and D-mannitol, respectively. In the process, two new stereogenic centers are created one of them being on an oxirane quaternary carbon. The excellent π-facial diastereoselection of the aldehydes combined with the diastereoselectivity of the carbene addition allowed us to synthesize the title compounds as single stereoisomers with well defined absolute configuration.

1. Introduction

C-Phosphorylated oxiranes are interesting compounds with some of them displaying relevant antibacterial activity.[1] The most relevant instance is the antibiotic phosphomycin, (1*R*,2*S*)-epoxypropylphosphonic acid,[2] whose discovery prompted significantly an increase in investigations in this field. Moreover, polyfunctionalized epoxides are very useful as synthetic building blocks to prepare a wide range of organic products.[3]

With these ideas in mind, beside the well-known synthetic methods to prepare oxiranes,[4] we recently studied and reported on the reactions of several aliphatic[5] and aromatic[6] aldehydes with [bis(diisopropylamino)phosphino]-(trimethylsilyl)carbene, **2**, to afford stereoselectively phosphino epoxides in high yields. These products have a *trans*-configuration regarding the relative disposition of the alkyl(aryl) and the phosphino groups. This stereoselectivity has been rationalized by means of theoretical calculations by invoking steric effects and stabilizing interactions in the transition states leading to *cis* or *trans*-epoxides.[7]

Carbene **2** is stabilized by the push–pull effect of the phosphino and the silylate substituents on the carbene center and has a remarkable behavior as a nucleophile[8] and as a base.[9] Its reaction with aldehydes can be envisaged as a [2+1] addition of the carbene to the carbonyl and is related to the Corey–Chaykovsky reaction.[4a] Nevertheless, in the reactions with aliphatic aldehydes, oxiranes were accompanied by olefinic compounds, presumably resulting from a [2+2] cycloaddition to produce an intermediate oxaphosphetene that rearranges rapidly to give a vinyl phosphonamide as a reaction by-product (Scheme 1).[5]

To further explore this chemistry, the asymmetric version of this reaction was considered, and we describe herein the first reactions of carbene **2** with enantiopure aliphatic aldehydes prepared from the chiral pool. In these processes, two new stereogenic centers are created, one being a quaternary carbon on the oxirane ring. Some models are offered to justify the preferred π-facial diastereoselection of the aldehyde that, combined with the diastereoselectivity of the addition, and allowed us to obtain the oxiranes as single stereoisomers.

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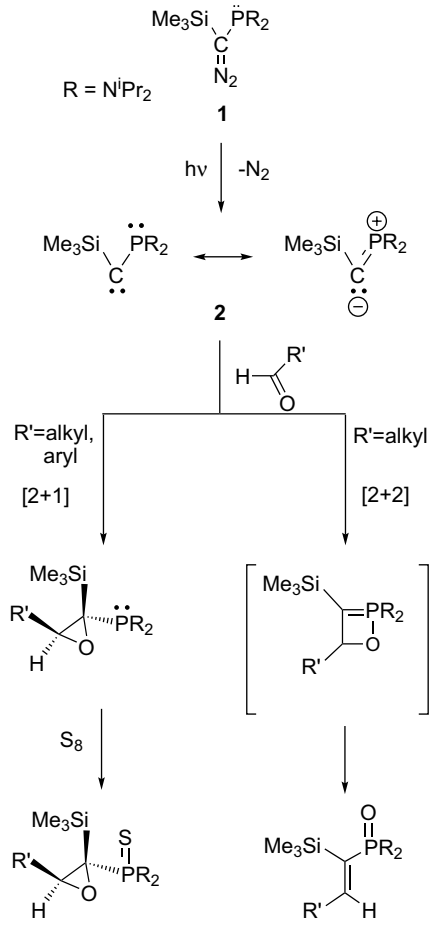
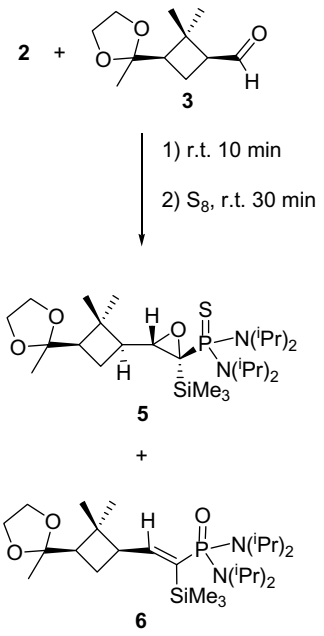


Scheme 1.



Scheme 2.

2. Results and discussion

The chiral aldehydes **3** and **4** were used as convenient models to investigate the stereoselectivity of these reactions, focusing attention on the π-facial diastereoselection. Compound **3** was synthesized from (−)-verbenone by using a protocol previously developed in our laboratory.[10] Aldehyde **4** is commercially available.

2.1. Reaction of carbene 2 with aldehyde 3

A pentane solution of the precursor diazocompound **1** was irradiated at −65 °C for 10 h to generate carbene **2** (the reaction can be monitored by ^{31}P NMR spectroscopy), and then aldehyde **3** (1 equiv) was added. After 10 min at room temperature, elemental sulfur was added to stabilize the phosphine by thiolation. Purification by flash column chromatography afforded oxirane **5** in 40% yield as a solid (Scheme 2).[11] X-ray diffraction structural analysis allowed the unequivocal assignment of configuration to the two new stereogenic centers as (2*S*,3*S*) as shown in Figure 1.[12] Vinyl phosphonamide **6** was also isolated in 5% yield. *E* stereochemistry was assigned to this compound on the basis of the coupling constant value $^{3}J_{H-P} = 32.6$ Hz by comparison with other similar products whose configuration had been unambiguously determined by X-ray analysis.[5]

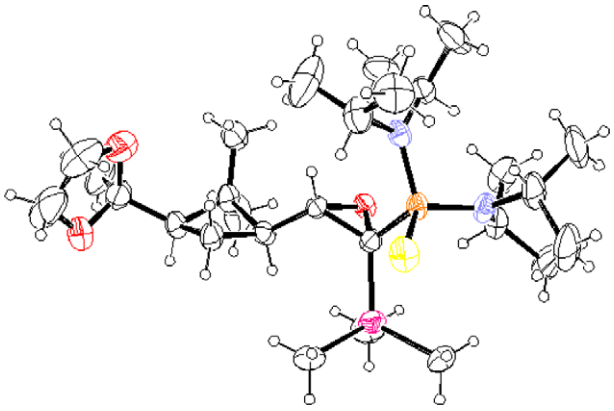


Figure 1. Structure of oxirane **5** as determined by X-ray structural analysis.

The stereochemistry observed in the formation of **5** can be rationalized by exclusive attack of the bulky carbene on the carbonyl *Si*-face, which is opposite to the cyclobutane *gem*-dimethyl group in conformer **3b** (Fig. 2). Theoretical calculations at the B3LYP/6-31G(d)[13] level using the GAUSSIAN 03[14] program, have led to two conformers **3a** and **3b**, the first one being slightly more stable by a Gibbs energy difference of 0.5 kcal mol^{-1}. We have located the transition states for the attack of the model carbene used in previous studies (R = NMe_2 in Scheme 1)[5,6] to the less hindered face of the carbonyl group in both conformers and the Gibbs activation energies for *Re*- and *Si*-attacks are 23.6 and 22.2 kcal mol^{-1}, respectively. This difference is compatible with the exclusive formation of one of the two possible diastereomers. A similar diastereoselection was observed in the reactions of olefins derived from **3** with diazoalkanes,[15,16] *N*-alkylhydroxylamines,[17] and nitromethane.[18]

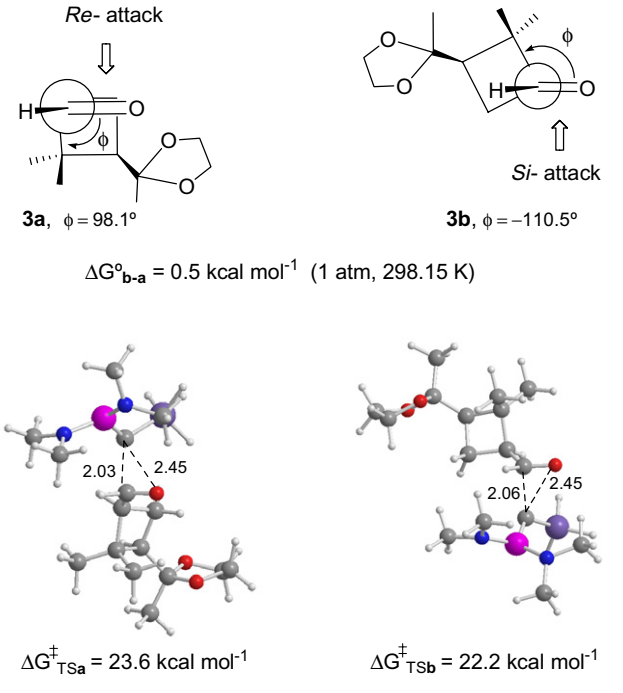


Figure 2. Calculated conformers **3a** and **3b** (top) and transition states for the attack to the less hindered carbonyl face in both conformers. Distances are expressed in angstroms (down).

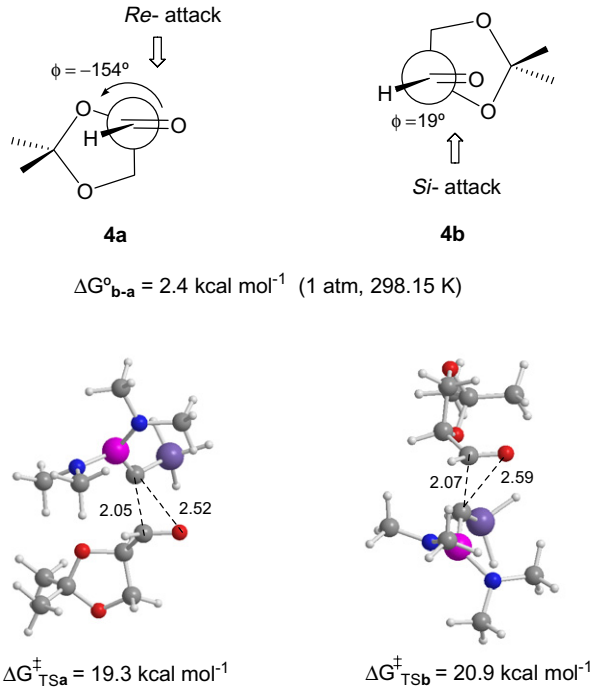
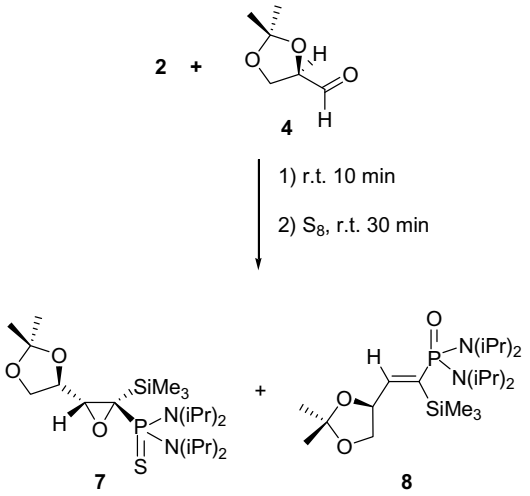


Figure 3. Calculated conformers **4a** and **4b** (top) and transition states for the attack to the less hindered carbonyl face in both conformers. Distances are expressed in angstroms (down).

2.2. Reaction of carbene 2 with aldehyde 4

In a similar manner, carbene **2** reacted with D-glyceraldehyde acetonide **4** to afford oxirane **7** and vinylphosphonamide **8** in 30% and 5% yield, respectively (Scheme 3).[11] Compound **7** was a solid which was unsuitable to submission to X-ray structural analysis. The configuration for the new stereogenic centers was assigned as (2*R*,3*R*) by assuming that the addition is most favorable on the π-face *anti* to the dioxolane methylene group (*Re*-face) in the most stable conformer as depicted in Figure 3. Theoretical calculations have led to conformers **4a** and **4b**. In this case, the Gibbs energy difference between both conformers is 2.4 kcal mol^{-1}, **4a** being the most stable one. This difference would be large enough to predict that the reaction with carbene **2** would lead to the exclusive formation of the diastereomer resulting from attack to the less hindered face of aldehyde **4** in the most stable conformer. In this case, we have also located the transition states for the attack of the model carbene and the corresponding Gibbs activation energies are 19.3 and 20.9 kcal mol^{-1} for the *Re*- and the *Si*-attacks, respectively. This result confirms the prediction based on the relative energies of **4a** and **4b**.

This result is in accordance with the stereochemical outcome of the addition of diazomethane[19] and diazo compound **1**[15] to chiral olefins derived from aldehyde **4**, which were previously investigated in our laboratory.



Scheme 3.

3. Conclusion

We have shown that the addition of carbene **2** to chiral aldehydes proceeds with total diastereoselection affording oxiranes as single stereoisomers, in enantiomerically pure form. The modest yields obtained are overcome by the simplicity of the reaction which offers an easy and fast synthetic entry to highly functionalized chiral epoxides with predictable stereochemistry. These compounds are versatile intermediates in organic synthesis and active investigation is carried out in our laboratory to use them in the preparation of other chiral phosphorylated molecules.

Acknowledgments

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11. Compound **5**: Crystals, mp 123–126 (methanol). $[\alpha]_D = +28.3$ (*c* 0.46, CH_2Cl_2). ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 86.6. ^1H NMR (250 MHz, $CDCl_3$): δ 0.32 (s, 9H, $Si(CH_3)_3$), 1.15 (s, 3H, *c*-2′-CH_3), 1.22 (s, 3H, *t*-2′-CH_3), 1.26 (s, 3H, $CH_{3\,ketal}$), 1.30–1.40 (m, 24H, $(CH_3)_2CHN$–), 1.75–1.98 (m, 3H, $H_{3'}$, $H_{4'a}$, $H_{4'b}$), 2.18–2.25 (m, 1H, $H_{1'}$), 3.16 (dd, $^3J_{H-P} = {}^3J_{H3-H1'} = 9.2$ Hz, 1H, H_3), 3.79–4.11 (m, 8H, $–OCH_2CH_2O–$ and $(CH_3)_2CHN$–). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 1.4 ($Si(CH_3)_3$), 17.8 (*c*-2′-CH_3), 21.2 ($C_{4'}$), 23.5 ($(CH_3)_2CHN$–), 24.8 (*t*-2′-CH_3), 31.8 ($CH_{3\,ketal}$), 41.1 and 41.2 ($(CH_3)_2CHN$ and $C_{1'}$), 49.8 ($C_{3'}$), 56.3 (d, $^2J_{C-P} = 70.6$ Hz, C_2), 61.9 (C_3), 63.5, and 65.4 ($–OCH_2CH_2O–$), 109.6 (C_{ketal}). EI (70 eV) HRMS: calcd for $C_{27}H_{55}N_2O_3SiPS$, 546.3440; found, 546.3444. Compound **6**: Dense oil. $[\alpha]_D = +8.6$ (*c* 1.00, CH_2Cl_2). ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 37.4. ^1H NMR (250 MHz,$CDCl_3$): δ 0.29 (s, 9H, $Si(CH_3)_3$), 1.11 and 1.12 (2s, 6H, *c*-2′-CH_3 and *t*-2′-CH_3), 1.20–1.28 (9s, 27H, $(CH_3)_2CHN$– and $CH_{3\,ketal}$), 1.70–2.01 (m, 2H, $2H_{4'}$), 2.19 (dd, $^3J_{H-H} = 11.1$ Hz, $^3J_{H-H} = 7.5$ Hz, 1H, $H_{3'}$), 2.85 (m, 1H, $H_{1'}$), 3.57 (m, 4H, $(CH_3)_2CHN$–), 3.89 (m, 4H, $–OCH_2CH_2O$), 6.81 (dd, $^3J_{H-P} = 32.6$ Hz, $^3J_{H-H} = 11.1$ Hz, 1H, H_2). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 2.4 ($Si(CH_3)_3$), 18.8 (*c*-2′-CH_3), 23.4–24.1 ($(CH_3)_2CHN$–), 24.1 (*t*-2′-CH_3), 29.4 ($C_{4'}$), 31.3 ($CH_{3\,ketal}$), 43.5 ($C_{2'}$), 44.5 (d, $^3J_{P-C} = 23.8$ Hz, $C_{1'}$), 46.2 (d, $^2J_{P-C} = 4.4$ Hz, $(CH_3)_2CHN$–), 46.4 (d, $^2J_{P-C} = 4.4$ Hz, $(CH_3)_2CHN$), 49.6 ($C_{3'}$), 63.4 and 65.1 ($–OCH_2CH_2O–$), 109.5 (C_{ketal}), 139.1 (d, $^1J_{C-P} = 108.7$ Hz, C_1), 157.2 (C_2). EI (70 eV) HRMS: (M+H) calcd for $C_{27}H_{55}N_2O_3SiP$, 514.3720. Experimental, 514.3730. Compound **7**: Crystals, mp 120–122 (from ether–pentane). $[\alpha]_D = -47.1$ (*c* 1.87, CH_2Cl_2). ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 84.2. ^1H NMR (250 MHz, $CDCl_3$): δ 0.35 (s, 9H, $Si(CH_3)_3$), 1.24–1.42 (m, 30H, $(CH_3)_2CHN$– and $2CH_{3\,dioxolane}$), 3.29 (dd, $^3J_{H-P} = {}^3J_{H-H} = 8.5$ Hz, 1H, H_3), 3.61 (m, 1H, $H_{4'}$), 3.96 (m, 5H, $H_{5'}$ and $(CH_3)_2CHN$–), 4.16 (dd, $^2J_{H-H} = 8.1$ Hz, $^3J_{H-H} = 6.0$ Hz, 1H,$H_{5'}$). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 1.2 ($Si(CH_3)_3$), 22.3–26.4 ($(CH_3)_2CHN$– and $2CH_{3\,dioxolane}$), 47.6 (d, $^2J_{P-C} = 5.5$ Hz, $(CH_3)_2CHN$), 49.0 (d, $^2J_{P-C} = 5.5$ Hz, $(CH_3)_2CHN$), 58.1 (d, $^1J_{C-P} = 71.5$ Hz, C_2), 62.8 (C_3), 68.6 ($C_{5'}$), 73.3 ($C_{4'}$). ESI-MS, *m*/*z* 479.2 ($M+H^+$). Compound **8**: Oil. $[\alpha]_D = -10.00$ (*c* 0.40, CH_2Cl_2). ^{31}P NMR (101.2 MHz, $CDCl_3$): δ 25.8. ^1H NMR (250 MHz, $CDCl_3$): δ 0.04 (s, 9H, $Si(CH_3)_3$), 1.21–1.34 (m, 24H, $(CH_3)_2CHN$), 1.38 (s, 3H, $CH_{3\,dioxolane}$), 1.41 (s, 3H, $CH_{3\,dioxolane}$), 3.42–3.65 (m, 5H, $(CH_3)_2CHN$– and $H_{5'}$), 4.22 (dd, $^2J_{H-H} = 8.2$ Hz, $^2J_{HH} = 6.5$ Hz, 1H, $H_{5'}$), 4.85 (tdd, $^3J_{HH} = {}^3J_{H-H} = 6.6$ Hz, $^4J_{H-P} = 2.9$ Hz, $H_{4'}$), 6.23 (dd, $^3J_{P-H} = 17.0$ Hz, $^3J_{H-H} = 7.0$ Hz, H_2). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 1.0 ($Si(CH_3)_3$), 23.1–23.7 ($(CH_3)_2CHN$–), 25.6 and 26.6 ($CH_{3\,dioxolane}$), 46.6 ($(CH_3)_2CHN$–), 68.1 ($C_{5'}$), 74.7 ($C_{4'}$), 109.6 ($C_{2'}$), 132.4 (d, $^1J_{C-P} = 140.2$ Hz, C_1), 135.0 (d, $^3J_{PH} = 6.7$ Hz, C_2). ESI-MS, *m*/*z* 447.3 ($M+H^+$).
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