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Cyclization of α,β,ψ,ω-Unsaturated Bisphosphonates Using Organolithium-Initiated Conjugate Addition–Michael Tandem Reaction

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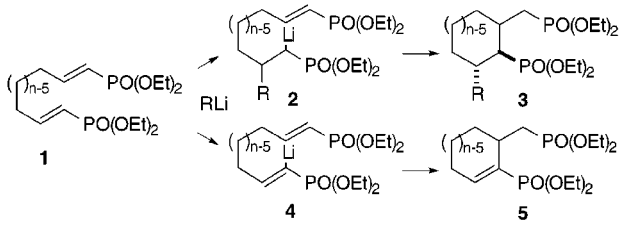
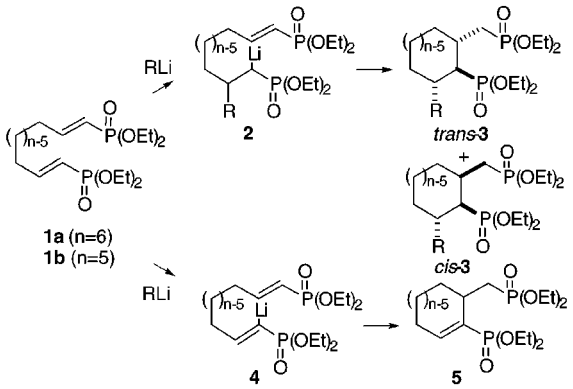
ABSTRACT



The reaction of α,β,ψ,ω-unsaturated bisphosphonates 1 with organolithiums afforded conjugate addition–Michael tandem cyclization products 3 and deprotonation–Michael cyclization products 5. Highly stereoselective deuteration of the intermediates proved the stereochemistry of lithium phosphonates 10, 13, and 15.

Alkylphosphonates are versatile isosteric analogues of natural phosphates, nucleotides, amino acids, and so on.[1] They are also useful synthetic precursors of olefins[2] as well as chiral phosphine ligands.[3] We have been engaged in studies aimed at an efficient synthetic application of lithium phosphonates and have already succeeded in the synthesis of allenes using α,β-unsaturated phosphonates[4] and of chiral olefins by an asymmetric Horner−Wadworth−Emmons reaction.[5] As part of our studies, we envisioned the development of an organolithium-initiated conjugate addition−Michael tandem cyclization of α,β,ψ,ω-unsaturated bisphosphonates **1**, giving the corresponding carbocycles **3** bearing two phosphonate moieties (Scheme 1). Contrary to the established double-Michael reaction of α,β,χ,ψ-unsaturated biscarboxylates for an efficient way to construct carbocycles,[6] application of a tandem methodology to **1** has not yet been developed.

Scheme 1. Cyclization of **1** with Organolithiums (RLi)



(1) For reviews on alkylphosphonates, see: (a) Engel, R. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; Chapter 11. (b) Engel, R. *Chem. Rev.* **1977**, *77*, 349−367. (c) Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, FL, 1983. (d) Rodan, G. A. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 375−388.

(2) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991.

(3) Chiral bisphosphine corresponding to (1*R*,2*R*)−**3**b (n = 5, R = H) has been reported in the rhodium-catalyzed asymmetric hydrogenation. Inoguchi, K.; Achiwa, K. *Synlett* **1991**, 49−51.

(4) Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 6428−6429.

(5) Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 515−517.

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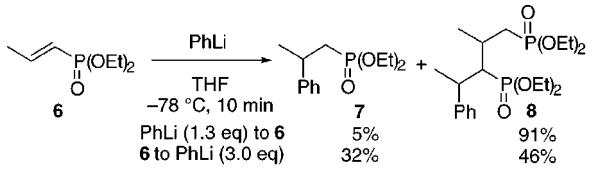
We began our studies by examining the reaction of diethyl propenylphosphonate **6** with phenyllithium (PhLi).[7] Addition of a cyclohexane−ether solution of 1.3 equiv of PhLi to a solution of **6** in THF at −78 °C gave the expected conjugate addition product **7** in only 5% yield together with **8** in 91% yield, which had arisen from the further Michael reaction of the lithium phosphonate intermediate with **6** (Scheme 2).[8]

Scheme 2. Conjugate Addition−Michael Reaction of **6**



Moderate improvement of the yield of **7** was realized by conducting the reaction under the reverse addition procedure. Thus, addition of **6** to a solution of 3 equiv of PhLi gave **7** in an increased 32% yield and **8** in a decreased 46% yield. These results clearly indicate that the lithium phosphonate produced by conjugate addition of PhLi to **6** becomes a good Michael donor, and also unsaturated phosphonate is a good Michael acceptor. Encouraged by the results, we examined the reaction of **1** with organolithiums. Unsaturated bisphosphonates **1** were readily prepared by the Horner−Wadsworth−Emmons reaction of methylenebisphosphonate with the corresponding dialdehydes.

Addition of 2.6 equiv of PhLi to a solution of **1a** ($n = 6$) in THF at −78 °C afforded a conjugate addition−Michael tandem cyclization product **3a** ($n = 6$, R = Ph) as a mixture of two separable isomers in 39% and 11% yields together with an α,β-unsaturated cyclic bisphosphonate **5a** ($n = 6$) in 18% yield (Table 1, entry 1). Improvement of the reaction

Table 1. Conjugate Addition−Michael Tandem Cyclization of **1** with Organolithiums

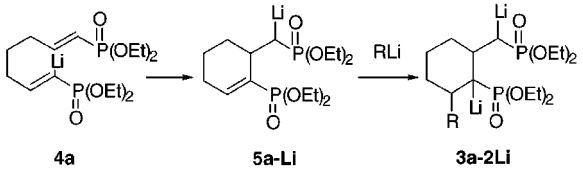
entry	**1**	*n*	R−Li	**3**+**5** (%)	*trans*-**3** (%)	*cis*-**3** (%)	**5** (%)
1[a]	**a**	6	Ph	68	39	11	18
2	**a**	6	Ph	85	64	9	12
3	**a**	6	1-Naph	94	58	0	39
4	**a**	6	2-Naph	71	44	0	27
5	**a**	6	Bu	58	20[b]	0	38
6	**b**	5	Ph	84	49	23	12

[a] A solution of PhLi was added to a solution of **1a**. [b] The stereochemistry was tentatively assigned by analogy for **3a** ($n = 6$, R = Ph).

was again observed by changing the reaction procedure. Thus, addition of **1a** to a solution of 2.2 equiv of PhLi in THF at −78 °C afforded *trans*- and *cis*-**3a** (R = Ph) in 64% and 9% yields together with 12% yield of **5a** (entry 2).

Formation of **5a** is attributable to a direct deprotonation of the vinylic α-proton of **1a**[9] to generate **4a** ($n = 6$) and subsequent intramolecular Michael cyclization (Schemes 1 and 3). Although it seems reasonable to speculate that

Scheme 3. Possible, but Ruled-Out, Formation of **3a** from **5a**



conjugate addition of PhLi to **5a** affords **3a** as shown in Scheme 3, conjugate addition of PhLi to **1a** and subsequent intramolecular Michael reaction of **2a** ($n = 6$, R = Ph) is responsible for the production of **3a**. Since the treatment of **5a** with 2.0 equiv of PhLi in THF at −78 °C failed to afford **3a** ($n = 6$, R = Ph), recovering **5a** unchanged, it became apparent that production of **3a** was independent of the formation of **5a**. Further experimental support was obtained by quenching the reaction with MeOD to afford monodeuterated **11** (vide infra, Figure 1). Double deuteration at the

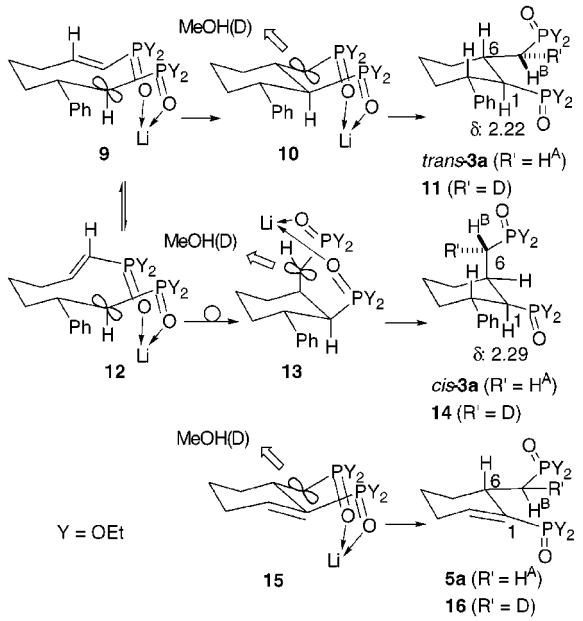


Figure 1. Stereoselective formation of *trans*- and *cis*-**3a** and deuteration into **11**, **14**, and **16**.

α-methylene and also α-methine carbons of the phosphonate **3a·2Li** was not observed (Scheme 3 and Figure 1). Unfavorably doubly lithiated **3a·2Li** should be responsible for the failure in the reaction of **5a·Li** with PhLi (Scheme 3).

(6) For the double-Michael reaction of unsaturated carbonyl compounds, see: (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159. (b) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139−3145.

(7) Michael addition of lithium enolates to α,β-unsaturated phosphonates has been reported: Darling, S. D.; Muralidharan, F. N.; Muralidharan, V. B. *Synth. Commun.* **1979**, *9*, 915−921.

The stereochemistries of *trans*- and *cis*-**3a** (n = 6, R = Ph) were determined by ^{1}H NMR.[10] Large coupling constants of the major **3a** between H1−H2 (10.4 Hz) and H1−H6 (10.9 Hz) clearly indicated that the major isomer is *trans*-**3a** as shown (Figure 1). On the other hand, large and small coupling constants of the minor **3a**, H1−H2 (11.6 Hz) and H1−H6 (3.9 Hz), indicated that the minor isomer is *cis*-**3**.

Formation of the major *trans*- and minor *cis*-**3a** is attributable to the inherent characteristics of lithium phosphonate. The conjugate addition reaction of PhLi with **1a** generates an equilibrium mixture of the lithium phosphonates **9** and **12** in which the lithium atom is coordinated by two oxygen atoms of the phosphonates and the lithium−oxygen bonds are inclined to the direction of the carbanionic carbon (Figure 1). The carbanionic carbon should be planar to the P═O double bond and the H−C (carbanionic carbon) bond is syn to the P═O bond due to steric reasons.[11] The structure **9** satisfies the above requirements and cyclizes smoothly to generate another lithium phosphonate **10**, which also satisfies the above requirements. Protonation of **10** results in the production of *trans*-**3a**. On the other hand, the structure **12** cyclizes to **13** with unfavorable concomitant rotation of the phosphate moieties to satisfy the above requirements. Protonation of **13** gives *cis*-**3a**.

The assumed structures **10** and **13** are characteristic of the lithium phosphonate. Support for these structures was obtained by highly stereoselective deuteration of **10**, **13**, and **15**. The tandem cyclization reaction of **1a** with PhLi was quenched with MeOD to afford **11**, **14**, and **16** as monodeuterated single diastereomers in 63%, 8%, and 13% yields (Figure 1, cf. entry 2). It is remarkable that only one of the methylene protons was stereoselectively deuterated.[12] These highly stereoselective deuterations are only possible from the fixed stereostructure of lithium phosphonates **10**, **13**, and **15**.

Naphthyl- and butyllithiums also initiated the tandem cyclization of **1** as shown in Table 1. It is noteworthy that the reactions with bulky naphthyllithiums gave only *trans*-**3a** (R = 1- and 2-Naph) free of the *cis* isomer, probably due to steric destabilization of the chelated structures corresponding to **12** or **13**. It is remarkable that three contiguous stereogenic centers were constructed in a perfect selectivity. Cyclization of **1b** (n = 5) with PhLi also proceeded to afford cyclopentylbisphosphonates **3b** (R = Ph) in 72% yield and **5b** (n = 5) in 12% yield.

In summary, the conjugate addition−Michael tandem cyclization of α,β,ψ,ω-unsaturated bisphosphonates was shown to be a versatile methodology for the construction of carbocycles bearing a bisphosphonate function. The methodology will provide a rapid entry into a variety of cyclic bisphosphonates in good stereoselectivity. Selective formation of **3** and **5** is a current focus of our study.

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Supporting Information Available: Typical experimental procedure, characterization data and NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991024H

(8) Attempted conjugate addition of organolithiums to propenylphosphonate **6** has been reported: Muller E. L.; Modro, T. A. *Bull. Soc. Chem. Fr*. **1993**, *130*, 668−672.

(9) Deprotonation of phenylethenylphosphonate at the α-position has been reported. Atta, F. M.; Betz, R.; Schmid, B.; Schmidt, R. R. *Chem. Ber*. **1986**, *119*, 472−481.

(10) ^{1}H NMR ($CDCl_3$, 500 MHz) presented in δ (ppm). *trans*-**3a**: 0.85, 1.23, 1.32 and 1.33 (each 3H, t, J = 7.0 Hz, $POCH_2CH_3$), 1.20−1.30 (1H, m, H5), 1.32−1.45 (2H, m, H3 and H4), 1.76 (1H, m, H4), 1.83 (1H, m, H3), 1.85 (1H, ddd, J = 18.3 (HA-P), 15.2 (HA-HB), 9.1 (HA-H6) Hz, HA7), 2.15−2.30 (1H, m, H6), 2.22 (1H, ddd, J = 19.3 (H1−P), 10.9 (H1−H6), 10.4 (H1−H2) Hz, H1) 2.40 (1H, m, H5), 2.83 (1H, ddd, J =10.7 (H2−H3), 10.4 (H2−H1), 4.2 (H2−H3) Hz, H2), 3.04 (1H, ddd, J = 21.0 (HB−P), 15.2 (HB−HA), 1.9 (HB−H6) Hz, HB7), 3.26 (1H, m, $POCH_2$-CH_3), 3.67 (1H, m, $POCH_2CH_3$), 3.92 (2H, m, $POCH_2CH_3$), 4.05−4.15 (4H, m, $POCH_2CH_3$), 7.13−7.28 (5H, m, Ph). *cis*-**3a**: 0.93, 1.21, 1.330, 1.332 (each 3H, t, J = 7.0 Hz, $POCH_2CH_3$), 1.47−1.59 (2H, m, H3 and H5), 1.60−1.70 (2H, m, $H_2$4), 1.83−1.90 (1H, m, H3), 2.18 (1H, ddd, J = 18.3, 15.6, 12.2 Hz, HA7), 2.20−2.30 (1H, m, H5), 2.29 (1H, dddd, J = 16.5 (H1−P1), 11.6 (H1−H2), 4.6 (H1−P7), 3.9 (H1−H6) Hz, H1), 2.42 (1H, ddd, J = 21.1, 15.6, 2.2 Hz, HB7), 2.75−2.85 (1H, m, H6), 2.90 (1H, dddd, J = 11.9 (H2−H3), 11.6 (H2−H1), 5.2 (H2−P1), 4.2 (H2−H3) Hz, H2), 3.01 and 3.53 (each 1H, m, $POCH_2CH_3$), 3.90 (2H, m, $POCH_2CH_3$), 4.11 (4H, m, $POCH_2CH_3$), 7.15−7.19 (1H, m, Ph), 7.25−7.29 (4H, m, Ph). **5a**: 1.33 (9H, t, J = 7.0 Hz, $POCH_2CH_3$), 1.34 (3H, t, J = 7.0 Hz, $POCH_2CH_3$), 1.65 (3H, m, $H_2$4 and H3), 1.76 (1H, ddd, J = 15.9, 11.9, 11.9 Hz, HA7), 2.04−2.25 (3H, m, $H_2$5 and H3), 2.43 (1H, ddd, J = 20.1, 15.9, 1.8 Hz, HB7), 2.81 (1H, m, H6), 4.08 (8H, m, $POCH_2CH_3$), 6.81 (1H, ddd, J = 22.3, 4.0, 4.0, H2).

(11) An X-ray crystallographic structure of lithium phosphonate has been reported: Denmark, S. E.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 2, 864−866.

(12) The compound **11** showed a double doublet at δ 3.00 (1H, dd, J = 20.4 (HB−P), 1.0 (HB−H6) Hz) which was assigned as HB7. A peak corresponding to HA (δ 1.85) of *trans*-**3a** (n = 6, R = Ph) disappeared, indicating the highly stereoselective deuteration of **10**.Compounds **14** and **16** showed the same NMR pattern. The protons HA and HB in *trans*- and *cis*-**3a** were assigned on the basis of the coupling constants which were reasonably simulated by the conformational analysis using MacroModel V6.5.