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Asymmetric synthesis of the cyclopentanones related to NCS and N1999A2 antitumor antibiotics

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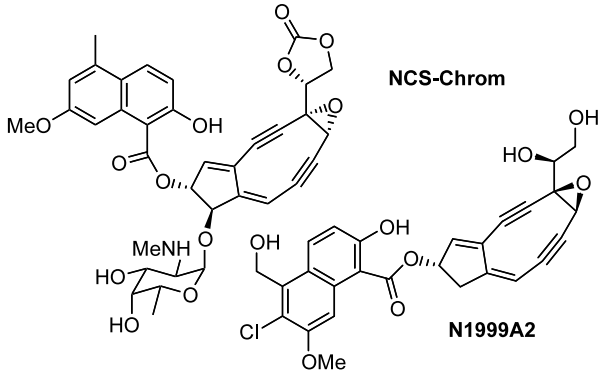
Abstract—Optically pure protected mono- or dihydroxylated cyclopentanones, precursors for the core of the antitumor antibiotics NCS and N1999A2, **1** and **2**, were obtained in six to eight steps with excellent overall yields (up to 52%).

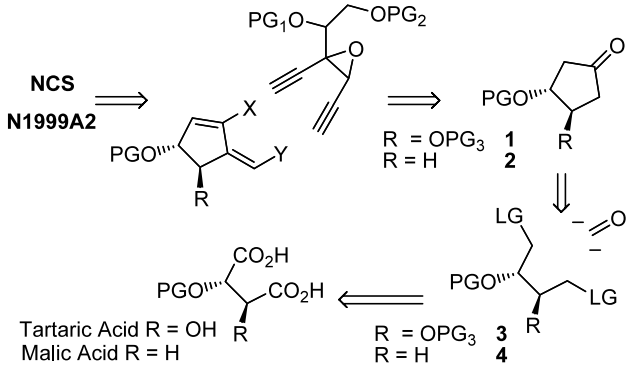
Neocarzinostatin Chromophore (NCS-Chrom; Scheme 1)[1] and N1999A2 (Scheme 1)[2] belong to the dienediyne (DEDY) class of antitumor antibiotics.[3] The potent biological activities of these DEDY and their unique structures have initiated increasing efforts from synthetic chemists,[4] which recently culminated with their, so far sole, synthesis.[5,6] A retrosynthetic analysis gives a possible expedient route towards the synthesis of NCS-Chrom. and related compounds based on coupling reactions between appropriate diethynyloxiranes and hydroxylated cyclopentenyl derivatives. Such a disconnection leads to two fragments of equal complexity each including a ring, two unsaturated bonds and one to three stereogenic centers, it would also provide the opportunity to use combinatorial tools at the coupling stage (Scheme 2).

As a prelude to the synthesis of NCS-Chrom[7] and analogs based on this strategy, we already reported on new conditions for coupling polyfunctionalized compounds[8] and for direct coupling of silylated alkynes.[9] We now described a convenient and rapid access to optically pure five-membered ring precursors of the NCS-Chrom and N1999A2 nuclei.

These functionalized cyclopentane derivatives can be derived from the corresponding hydroxylated cyclopentanones **1**–**2**. These ketones could be obtained through a ring closure reaction between a formyl dianion synthon and mono- or dihydroxylated butane derivatives **3** or **4** (Scheme 2). These chiral derivatives could be conveniently prepared from either tartaric acid or malic acid. Since all stereoisomers of these acids are commercially available, any stereoisomers of **1** and **2** could be



Scheme 1. Structures of NCS-Chrom. and N1999A2.



Scheme 2. Retrosynthetic analysis of NCS and N1999A2.

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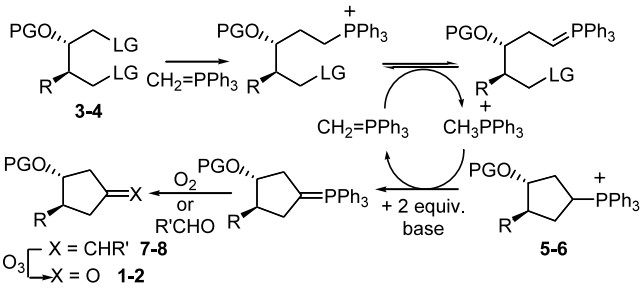
obtained and used for structure–activity relationship studies. The two protecting groups in **1** must be different in order to later on functionalize it.

Despite their usefulness especially as intermediate for prostanoïds syntheses, there are only a few reports dealing with the synthesis of **1** or its enantiomer, protected or not. Surprisingly enough, only one synthesis of **2** was mentioned in a paper dealing with the kinetic resolution of racemic allylic alcohols.[10] The four known syntheses of **1** or *ent*-**1** started from (*R*,*R*)- or (*S*,*S*)-tartaric acid and were based on a common strategy identical in essence to the one disclosed above. They, however, led to C_2-symmetrical compounds. Gero et al. described a rather lengthy procedure (12 steps, overall yield unknown).[11] A similar procedure was reported by Corey et al.[12] More recently, Rokach et al. and Suffert et al. reported improved versions of these routes (7–8 steps, 33–34% overall yield).[13,14] In all cases, various formyl anion equivalents were investigated with limited success[11,13,14] and the final recovery of the ketone from the masked cyclopentanone derivatives so obtained proved to be always troublesome, usually low yielding and giving mixtures.[13,14] In a synthesis of 1-nitro-1-cyclopentenes, was mentioned a lengthy access to monoprotected **1** from D-glucose (11 steps, 34% overall yield).[15]

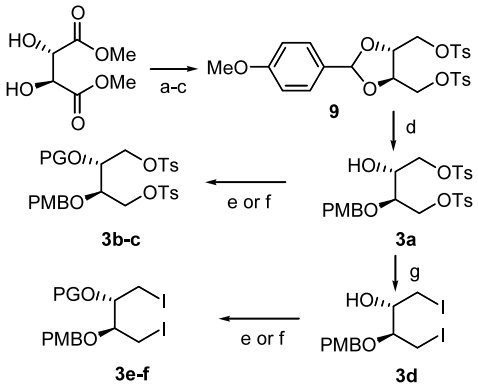
To overcome these problems and nevertheless have a rapid and scalable route to **1** and **2**, we decided to explore the potential of another type of formyl anion equivalents, i.e. the methylenetriphenylphosphorane. During his extensive studies on alkylidenephosphorane reactivity,[16] Bestmann described a ring closure reaction of 1,ω-dibromo or ditosyloxyalkanes by addition of alkylidene phosphorane.[17] It is worth noting that the cyclic phosphonium salt so obtained could be isolated and further oxidized to the corresponding cycloalkanone.[18] Therefore, this sequence would offer a rapid access toward **1** and **2**, and furthermore, would be the *first application* of this reaction toward natural product synthesis.

Applied to our goal, this cyclization requires that 2 equiv. of methylenetriphenylphosphorane,[19] must be added to the mono- or dihydroxylated butanes **3** or **4** (Scheme 3). The so formed cyclic phosphonium **5** or **6** could then be isolated and oxidized by oxygen after conversion to the corresponding ylide or it could be in situ treated with base then with an aldehyde. The corresponding alkylidene cyclopentane **7** or **8** can then be ozonized to the desired cyclopentanone **1** or **2**.

The synthesis of **1** started from (*S*,*S*)-dimethyl tartrate (Scheme 4). In order to differentiate its hydroxyl groups, a *para*-methoxybenzylidene group was introduced since it can be later reductively cleaved. After quantitative protection of the diol and reduction of the diester moiety through a known procedure,[20] the so formed diol was fully tosylated by an excess of tosyl chloride in pyridine giving **9** with an excellent overall yield. This bistosyl ketal was best opened with DIBAH in toluene at room temperature.[21] The corresponding



Scheme 3. Mechanism of the cyclization with methylene–triphenylphosphorane.

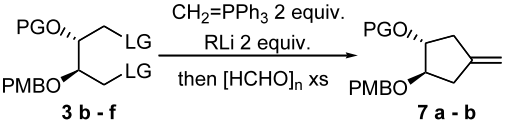


Scheme 4. *Reagents and conditions*: (a) pMeOPhCHO, CSA, PhH; (b) $NaBH_4$, LiCl, THF; (c) TsCl, Py, 93% over three steps; (d) DIBAH, Tol, 89%; (e) DHP, PPTS, CH_2Cl_2 (PG = THP, **3b** 96%, **3e** 100%); (f) CH_2=CHOEt, PPTS, CH_2Cl_2 (PG = EE: **3c** 98%, **3f** 100%); (g) NaI, Me_2CO, 99%.

alcohol **3a** was then protected, only the tetrahydropyranyl (THP)[22] and ethoxyethyl (EE)[23] groups could however be introduced.[24] The protected bistosylates **3b–c** were obtained in almost quantitative yields using conventional reaction conditions. In order to check the scope of the Bestmann cyclization, we also prepared the iodinated analogs **3e–f** using usual conditions.[25] With these butane derivatives bearing different protecting and leaving groups in hand, we then explored the key cyclization step. Selected results of our screening experiments are shown in Table 1.

We were unable to isolate the expected cyclopentanone **1** from the complex mixtures obtained in any of the conditions described for the direct oxidation of phosphonium ylides.[17,18] We thus trapped the phosphonium ylide in situ formed after addition of 2 equiv. of base by simply adding excess paraformaldehyde to the reaction mixture. The methylenecyclopentane derivatives **7a–b** (PG = THP or EE respectively) were thus isolated in moderate to good yields depending on the conditions (Table 1).[26] The right combination of leaving and protecting groups seemed important for an efficient cyclization (entries 1, 3 versus 2, 4), the best combination being iodide and EE respectively. However, the most critical factor proved to be the nature of the base, phenyllithium always giving the best results (see 1a, entry 7 versus 4).[27]

Table 1. Cyclization of tartrate derivatives[27]



Entry	LG	PG		Conditions	Yields (%)[a]
1	OTs	THP	**3b**	^{n}BuLi, THF, 66°C	32
2	I	THP	**3e**	^{n}BuLi, THF, 66°C	35
3	OTs	EE	**3c**	^{n}BuLi, THF, 66°C	25
4	I	EE	**3f**	^{n}BuLi, THF, 66°C	59
5	OTs	THP	**3b**	PhLi, THF, rt	55
6	I	EE	**3f**	PhLi, THF, rt	65
7	I	EE	**3f**	PhLi, THF, 66°C	79

[a] Yields of pure isolated products.

S-Malic acid could be transformed in a similar way. After esterification, the free hydroxyl group in **10** was protected with different protecting groups without any problem. The benzyl group was best introduced with the benzyl transfer conditions catalyzed by Lewis acid.[28] The protected diesters **11a–c** were then reduced and the corresponding diols tosylated leading to **4a–c** in good yields. The diiodo derivatives **4d–f** were also prepared (Scheme 5).

These butane derivatives were then submitted to cyclization (Table 2). In these series, the leaving group as well as the protecting group have a dramatic influence on the reaction outcome. The compounds protected with a silyl group could not be readily converted to the expected methylenecylopentane **8b** (entries 2, 5), while the ethoxyethyl group only allowed for low to moderate yields (entries 1, 4). The benzyl group proved to be the best one giving up to 61% of the expected cyclized product **8c** (entries 3, 6). Here again, the iodides always gave the best results (entries 4–6 versus 1–3).

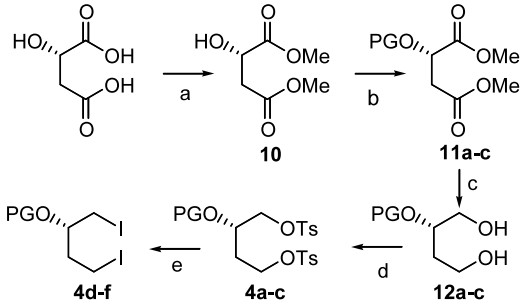
The cyclization proved to be more efficient in the tartaric series than in the malic series but in each case, mono- or dihydroxylated methylenecyclopentanes **7** or **8** can be rapidly obtained (5–7 steps). The corresponding ketones **1** or **2** were then conveniently obtained in good yields (77–88%) through ozonolysis.

In conclusion, the above-mentioned results clearly demonstrated that the Bestmann cyclization first can be applied to highly functionalized compounds, and second is a good alternative to other methods leading to cyclopentane derivatives. Indeed, the protected mono- or dihydroxylated cyclopentanones **1** or **2** were obtained in 6–8 steps with excellent overall yields (up to 52%)

Supplementary material

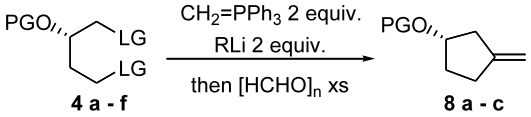
Typical procedure for the cyclization: To a suspension of $MePh_3P^+Br^-$ (2 equiv.) in THF (0.12 M) was added a commercial solution of PhLi (2 equiv.). After 30 min, a 0.25 M THF solution of **3** or **4** (1 equiv.) was added and the resulting mixture was refluxed for 16 h. A precipitate gradually formed and the solution color discharged After cooling to room temperature, PhLi (2 equiv.) was added again. The suspension vanished to a dark solution. After 5 min, excess of formaldehyde was added. The color discharged again. After stirring for 1 h, water was added and the mixture was extracted three times with diethyl ether. The combined organic layers were then dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography.

7a (PG = THP; mixture of diastereoisomers): ^{1}H NMR (250 MHz, $CDCl_3$): 1.48–1.90 (6H, m), 2.22–2.46 (2H, m), 2.61–2.85 (2H, m), 3.46–3.58 (1H, m), 3.81 (3H, s), 3.81–4.05 (2H, m), 4.07–4.32 (1H, m), 4.51 (2H, br. s) and 4.54 (1H, d, J = 11.0) 4.58 (1H, d, J = 11.0), 4.66–4.80 (1H, m), 4.88–4.93 (2H, m), 6.87 and 6.88 (2H, d, J = 8.6), 7.26 and 7.28 (2H, d, J = 8.6); ^{13}C NMR (62 MHz, $CDCl_3$): 19.44 and 19.74 (q), 25.44 (t), 30.92 and 31.01 (t), 36.40 and 36.68 (t), 37.09 and 37.96 (t), 55.24 (q), 62.32 and 62.69 (t), 70.87 and 70.95 (t), 79.52 and 81.04 (d), 82.66 and 82.98 (d), 96.95 and 98.67 (d), 107.64 (t), 113.73 (d), 129.09 (d), 130.66 and 130.84 (s), 146.28 and 146,78 (s), 159.08 and 159.14 (s).



Scheme 5. *Reagents and conditions*: (a) AcCl, MeOH, 98%; (b) **11a** PG = EE: CH_2=CHOEt, PPTS, CH_2Cl_2, 98%; **11b** PG = TPS: ^{t}BuPh$_2$SiCl, DMAP, Et_3N, CH_2Cl_2, 93%; **11c** PG = Bn: BnOC(=NH)CCl$_3$, CH_2Cl_2, 79%; (c)NaBH$_4$, LiCl, THF (**12a** 96%, **12b** 79%, **12c** 78%); (d) TsCl, Py (**4a** 90%, **4b** 78%, **4c** 79%); (e) NaI, Me_2CO (**4d** 69%, **4e** 79%, **4f** 88%).

Table 2. Cyclization of malate derivatives



Entry	LG	PG		Conditions	Yields (%)[a]
1	OTs	EE	**4a**	PhLi, THF, 66°C	20
2	OTs	TPS	**4b**	PhLi, THF, 66°C	0
3	OTs	Bn	**4c**	PhLi, THF, 66°C	42
4	I	EE	**4d**	PhLi, THF, 66°C	45
5	I	TPS	**4e**	PhLi, THF, 66°C	5
6	I	Bn	**4f**	PhLi, THF, 66°C	61

[a] Yields of pure isolated products.

7b (PG = EE; mixture of diastereoisomers): ^{1}H NMR (250 MHz, $CDCl_3$): 1.19 (3H, t, J = 7.1), 1.31 (3H, d, J = 5,3), 2.24–2.40 (2H, m), 2.62–2.80 (2H, m), 3.39–3.54 (1H, m), 3.59–3.73 (1H, m), 3.81 (3H, s), 3.84–4.00 (1H, m), 4.08–4.19 (1H, m), 4.49 and 4.52 (2H, br. s), 4.74 and 4.80 (1H, q, J = 5.3), 4.86–4.93 (2H, m), 6.88 and 6.89 (2H, d, J = 8.6), 7.26 (2H, d, J = 8.6); ^{13}C NMR (62 MHz, $CDCl_3$): 15.19 (q), 20.58 and 20.67 (q), 36.60 and 36.72 (t), 37.26 and 37.82 (t), 55.16 (q), 60.62 (t), 70.95 (t), 78.98 and 79.80 (d), 83.13 (d), 98.86 and 99.55 (d), 107.74 (t), 113.70 (d), 129.06 (d), 130.54 (s), 146.05 and 146,35 (s), 159.11 (s).

8a (PG = EE; mixture of diastereoisomers): ^{1}H NMR (200 MHz, $CDCl_3$): 1.21 (3H, t, J = 7.1), 1.30 (3H, d, J = 5.4), 1.65–2.08 (2H, m), 2.14–2.62 (4H, m), 3.49 (2H, q, J = 7.1) and 3.62 (2H, q, J = 7.1), 4.20 (1H, m), 4.72 (1H, q, J = 5.4) and 4.76 (1H, q, J = 5.4), 4.88 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): 15.36 (q), 20.69 (q), 30.22 and 30.39 (t), 32.05 and 32.34 (t), 35.60 and 36.28 (t), 60.31 (t), 76.35 (t), 98.58 and 98.76 (d), 115.79 (d), 140.17 (s); I.R. (neat): 1601, 1382, 1244, 1098, 987.

8c (PG = Bn): ^{1}H NMR (200 MHz, $CDCl_3$): 1.83–1.94 (2H, m), 2.18–2.64 (4H, m), 4.08 (1H, m), 4.53 (2H, s), 4.91 (2H, m), 7.22–7.39 (5H, s); ^{13}C NMR (50 MHz, $CDCl_3$): 30.15 (t), 32.10 (t), 39.51 (t), 70.78 (t), 79.89 (d), 106.51 (t), 127.51 (d), 127.65 (d), 128.41 (d), 138.88 (s), 149.85 (s).

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References

1. (a) Ishida, N.; Miyazaki, K.; Kumagai, K. M.; Rikimura, M. *J. Antibiot*. **1965**, *18*, 68–76; (b) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett*. **1985**, *26*, 331–334.
2. (a) Ishii, M.; Ando, T.; Kajiura, T.; Kameyama, T.; Nihey, Y. *Jpn. Kokai Tokkyo Koho* JP 07291955; *Chem. Abstr*. **1996**, *124*, 115564h; (b) Ando, T.; Ishii, M.; Kajiura, T.; Kameyama, T.; Miwa, K.; Sugiura, Y. *Tetrahedron Lett*. **1998**, *39*, 6495–6498.
3. **Kedarcidin**: (a) Hofstead, S. J.; Matson, J. A.; Malacko, A. R.; Marquard, H. *J. Antibiot*. **1992**, *45*, 1250–1254; (b) Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Golik, J.; Colson, K. L.; Huang, S.; Klohr, S. E.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc*. **1992**, *114*, 7946–7948; **C-1027**: (c) Zhen, Y.-S.; Ming, X.-Y.; Yu, B.; Otani, T.; Saito, H.; Yamada, Y. *J. Antibiot*. **1989**, *42*, 1294–1298; (d) Yoshida, K.-I.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett*. **1993**, *34*, 2637–2640; **Maduropeptin**: (e) Hanada, M.; Ohkuma, H.; Yonemoto, T.; Tomita, K.; Ohbayashi, M.; Kamei, H.; Miyaki, T.; Konishi, M. M.; Kawaguchi, H.; Forenza, S. *J. Antibiot*. **1991**, *44*, 403–414; (f) Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Zein, N.; Langley, D. R.; Lee, M.; Matson, J. A.; Doyle, T. W. *J. Am. Chem. Soc*. **1994**, *116*, 9351–9352.
4. For recent reviews, see: (a) Nicolaou, K. C.; Smith, A. L. In *Modern Acetylene Chemistry*, Stang, P. J.; Diederich, F., Eds.; VCH: Weinheim, 1995; pp. 203–283; (b) Lhermitte, H.; Grierson, D. S. *Contemporary Organic Synthesis*, Parts 1 and 2, 1996; pp. 41–63 and 93–124; (c) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453–6518.
5. (a) Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y.; Kuo, E. Y. *J. Am. Chem. Soc*. **1998**, *120*, 5319–5320; (b) Myers, A. G.; Glattar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J.-N. *J. Am. Chem. Soc*. **2002**, *124*, 5380–5401.
6. (a) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc*. **2001**, *123*, 2887–2888; (b) Kobayashi, S.; Ashizawa, S.; Takahashi, Y.; Sugiura, Y.; Nagaoka, M.; Lear, M.; Hirama, M. *J. Am. Chem. Soc*. **2001**, *123*, 11294–11295.

7. For related approaches towards NCS Chrom., see: (a) Nakatani, K.; Arai, K.; Hirayama, N.; Matsuda, F.; Terashima, S. *Tetrahedron* **1992**, *48*, 633–650; (b) Nakatani, K.; Arai, K.; Yamada, K.; Terashima, S. *Tetrahedron* **1992**, *48*, 3045–3060; (c) Suffert, J.; Brückner, R. *Synlett* **1994**, 51–53.
8. (a) Bertus, P.; Pale, P. *Tetrahedron Lett*. **1996**, *37*, 2019–2022; (b) Bertus, P.; Pale, P. *Tetrahedron Lett*. **1997**, *38*, 8193–8196; (c) Bertus, P.; Pale, P. *J. Organomet. Chem*. **1998**, *567*, 173–180; (d) Halbes, U.; Bertus, P.; Pale, P. *Eur. J. Org. Chem*. **2001**, 4391–4393; (e) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett*. **2001**, *3*, 1661–1664.
9. (a) Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett*. **2001**, *42*, 8641–8644; (b) Halbes, U.; Pale, P. *Tetrahedron Lett*. **2002**, *43*, 2039–2042.
10. Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R. *J. Org. Chem*. **1988**, *53*, 708–710.
11. Barrière, F.; Barrière, J.-C.; Barton, D. H. R.; Cleophax, J.; Gateau-Olesker, A.; Géro, S. D.; Tadj, F. *Tetrahedron Lett*. **1985**, *26*, 3119–3120.
12. Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett*. **1986**, *27*, 2199–2202.
13. Khanapure, S.; Najafi, N.; Manna, S.; Yang, J.; Rokach, J. *J. Org. Chem*. **1995**, *60*, 7548–7551.
14. Raeppel, S.; Toussaint, D.; Suffert, J. *Synlett* **1997**, 1061–1062.
15. Torii, S.; Inokuchi, T.; Oi, R.; Kondo, K.; Kobayashi, T. *J. Org. Chem*. **1986**, *51*, 254–256.
16. Bestmann, H. J. *Angew. Chem., Int. Ed*. **1965**, *4*, 645–660 and 830–838.
17. Bestmann, H. J.; Kranz, E. *Chem. Ber*. **1969**, *102*, 1802–1815.
18. (a) Bestmann, H. J.; Kratzer, O. *Chem. Ber*. **1963**, *96*, 1899–1908; (b) Bestmann, H. J.; Armsen, R.; Wagner, H. *Chem. Ber*. **1969**, *102*, 2259–2269.
19. The use of one equivalent of methylenephosphorane and further treatment by bases did provide cyclized products but in lower yield. Metallated methylenephosphorane (Corey, E. J.; Kang, J. *J. Am. Chem. Soc*. **1982**, *104*, 4724–4725; Corey, E. J.; Kang, J.; Kyler, K. J. *Tetrahedron Lett*. **1985**, *26*, 555–558) did not yield an efficient cyclization.
20. Somfai, P.; Olsson, R. *Tetrahedron* **1993**, *49*, 6645–6650.
21. Takano, S.; Akiyama, M.; Satoh, S.; Ogasawara, K. *Chem. Lett*. **1983**, 1593–1596.
22. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem*. **1977**, *42*, 3772–3774.
23. Fukusawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett*. **1987**, *28*, 4303–4306.
24. From the common silyl groups, only the triethyl- and trimethylsilyl could be introduced, but in low yield. The bulkiness of the reactive intermediate as well as the one of the hydroxyl group in **3a** might account for this limitation.
25. Tipson, R. S.; Clapp, M. A.; Cretcher, L. H. *J. Org. Chem*. **1947**, *12*, 133.
26. As judged from TLC, these cyclization reactions are quite clean. No double substitution product was detected using our conditions as far as judged from NMR of the crude mixture.
27. The reason why PhLi is the most effective base among those investigated is still unclear.
28. Wessel, H. P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2249.