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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8129–8131

Synthesis of isotetronic acids by cyclization of 1,3-bis(trimethylsilyloxy)alk-1-enes with oxalyl chloride

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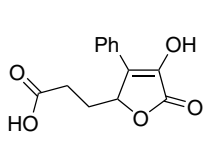
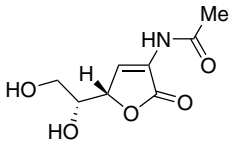
Received 4 August 2005; revised 20 September 2005; accepted 21 September 2005
Available online 7 October 2005

Abstract—Isotetronic acids were regioselectively prepared by cyclization of 1,3-bis(trimethylsilyloxy)alk-1-enes with oxalyl chloride.

Isotetronic acids and butenolides are of great pharmacological relevance and occur in a number of natural products:[1] for example, (+)-leptosphaerin represents a metabolite of the marine ascomycete *Leptosphaeria oraemaris*[2a] and compound WF-3681 represents an aldose reductase inhibitor produced by *Chaetomella raphigera*.[2b] Isotetronic acid derivatives have been used also as key intermediates during the synthesis of (−)-tetrodotoxin,[3a] 6-thiosialic and neuraminic acids,[3b–e] nactins[4a] or erythronolide A.[4b] Ascorbic acid derivatives[5a] represent synthetic precursors of (+)- and (−)-eldanolide,[5b] antileukaemic lignans, such as (+)-*trans*-burseran[5c] and (−)-isostegane,[5c] (+)- and (−)-steganacin,[5d] (−)-verrucarinolactone[5e] and chrysanthemic acid analogues. Although a number of synthetic approaches to isotetronic acids are known,[6,7] the development of new and efficient methods is of considerable current interest. The methodology reported herein provides a convenient and inexpensive approach to a variety of functionalized isotetronic acids from readily available starting materials. The reactions proceed in good yields and with very good regioselectivity and are convenient to be carried out.



WF-3681



(+)-Leptosphaerin

Oxalyl derivatives represent useful synthetic building blocks for the synthesis of oxygen heterocycles: Saalfrank and co-workers have reported the synthesis of 2,3-dioxo-2,3-dihydrofurans by cyclization of 1,3-dicarbonyl compounds with oxalyl chloride.[8] We have reported an efficient approach to α-hydroxy-γ-alkylidenebutenolides by cyclization of 1,3-bis-silyl enol ethers—masked 1,3-dicarbonyl dianions—with oxalyl chloride.[9] Herein, we wish to report a convenient one-pot synthesis of isotetronic acids by what are, to the best of our knowledge, the first cyclizations of oxalyl chloride with 1,3-bis(trimethylsilyloxy)alk-1-enes, which can be regarded as masked dianions of 3-hydroxyesters.[10]

The cyclization of oxalyl chloride with 1,3-bis(trimethylsilyloxy)alk-1-ene **2a**, available by reaction of the dianion of **1a** with trimethylchlorosilane,[11] afforded the isotetronic acid **3a**. After careful optimization of the reaction conditions (Table 1), **3a** was isolated in up to 54% yield. Interestingly, the best results were obtained when the reaction was carried out *without* the presence of a Lewis acid (entry 7, 1:1 stoichiometry, 18 h, $-78 \rightarrow 20$ °C, $c = 0.1$ M).[12] In contrast, the cyclization of 1,3-bis-silyl enol ethers with oxalyl chloride requires the use of catalytic amounts of Me_3SiOTf.[9] On the other hand, the reaction of 1,3-bis-silyl enol ethers with simple acid chlorides proceeds best in the absence of Lewis acid;[13] the same is true for

Keywords: Butenolides; Cyclizations; Isotetronic acids; Oxalyl chloride; Silyl enol ethers.
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0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.09.137

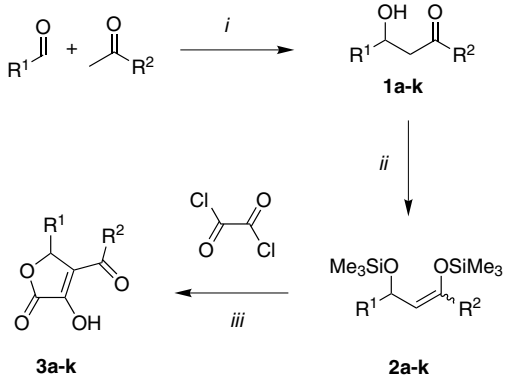
Table 1. Optimization of the synthesis of **3a**

Entry	Lewis acid (equiv)	$(COCl)_2$ (equiv)	*c* (**2a**) [M]	*t* [h], *T* [°C]	% (**3a**)[a]
1	Me_3SiOTf (0.5)	2.0	0.12	0.5, −78; 96, 20	51
2	Me_3SiOTf (0.5)	2.5	0.075	0.5, −78; 2, 50	14
3	Me_3SiOTf (0.5)	1.3	0.15	18, 20	50
4	Me_3SiOTf (1.0)	1.3	0.12	0.5, −78; 96, 20	53
5	Me_3SiOTf (4.0)	4.3	0.03	72, −78 → 20	30
6	Me_3SiOTf (4.0)	4.3	0.03	72, 0 → 20	23
7	None	1.0	0.10	18, −78 → 20	54
8	$BF_3{\cdot}OEt_2$ (2.0)	1.3	0.12	0.5, −78; 96, 20	40
9	$TiCl_4$ (2.0)	1.3	0.12	72, −78 → 20	0[b]
10	$TiCl_4$ (2.0)	1.3	0.12	72, −78 → 20	0[b]

[a] Isolated yields.
[b] Complex mixture.

the condensation of simple silyl ketene acetals with oxalyl chloride.[14]

The preparative scope of our methodology was studied (Scheme 1, Table 2). The 1,3-bis(trimethylsilyloxy)alk-1-enes **2a**–**k** were prepared by generation of the dianions of the 3-hydroxyalkanoates **1a**–**k**, which are available by aldol reaction of ethyl and methyl acetate with the corresponding aldehydes. The alkyl-substituted isotetronic acids **3a**–**i** were prepared from **2a**–**i**. All products were isolated (except for **3h**) in good yields. The cyclization

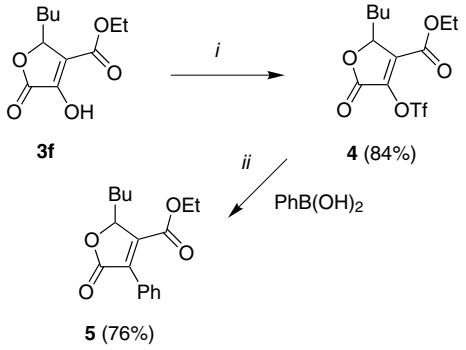


Scheme 1. Synthesis of isotetronic acids **3a**–**k**. Reagents and conditions: (i) LDA, THF, 5 min, −78 °C; (ii) (1) LDA (2.2 equiv), THF, 1 h, −78 °C, (2) Me_3SiCl (2.5 equiv), −78 → 20 °C, 24 h; (iii) $(COCl)_2$ (1.0 equiv), −78 → 20 °C, 18 h.

Table 2. Products and yields

3	R^1	R^2	% (**3**)[a]
a	Me	OEt	54
b	Me	OMe	52
c	Et	OEt	77
d	*n*Pr	OEt	71
e	*i*Pr	OEt	54
f	*n*Bu	OEt	75
g	*i*Bu	OEt	63
h	*t*Bu	OMe	19
i	*n*Hex	OMe	61
j	CH=CH_2	OEt	34
k	Ph	OEt	62

[a] Isolated yields.



Scheme 2. Synthesis of **5**. Reagents and conditions: (i) Tf_2O, pyridine, −78 → −10 °C; (ii) $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), dioxane, reflux.

of 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,4-pentadiene (**2j**) with oxalyl chloride afforded the vinyl-substituted isotetronic acid **3j**. The phenyl-substituted isotetronic acid **3k** was prepared from 1-ethoxy-1,3-bis(trimethylsilyloxy)-3-phenylprop-1-ene (**2k**). All transformations were carried out without the presence of a Lewis acid.

The hydroxy group of the isotetronic acid was successfully functionalized by transition metal catalyzed cross-coupling reactions: for example, **3f** was transformed into enol triflate **4**. The Suzuki reaction of **4** with phenylboronic acid afforded butenolide **5** in good yield (Scheme 2).

Our current studies are directed towards the synthesis of enantiomerically pure isotetronic acids from enantiomerically pure 3-hydroxyesters.

Acknowledgement

Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

References and notes

1. For reviews of butenolides, see: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; (b) Pattenden, G. *Prog. Chem. Nat. Prod.* **1978**, *35*, 133; (c) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287.

2. (a) Pallenberg, A. J.; White, J. D. *Tetrahedron Lett.* **1986**, 5591; (b) Namiki, T.; Nishikawa, M.; Itoh, Y.; Uchida, I.; Hashimoto, M. *Tetrahedron Lett.* **1987**, 1400.
3. (a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510; (b) Mack, H.; Brossmer, R. *Tetrahedron* **1998**, *54*, 4521; (c) Mack, H.; Brossmer, R. *Tetrahedron Lett.* **1992**, *33*, 1867; (d) Lafont, D.; Hoch, M.; Schmidt, R. R. *J. Carbohydr. Chem.* **1986**, *5*, 601; (e) Holmquist, L. *Acta Chem. Scand.* **1971**, *25*, 712.
4. (a) Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017; for the synthesis of erythronolide A, see: (b) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565.
5. (a) Vekemans, J. A. J. M.; Franken, G. A. M.; Dapperens, C. W. M.; Godefroi, E. F. G. *J. Org. Chem.* **1988**, *53*, 627; (b) Vigneron, J. P.; Meric, R.; Larcheveque, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagetti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521; (c) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303; (d) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311; (e) Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737.
6. Enders, D.; Dyker, H.; Leusink, F. R. *Chem. Eur. J.* **1998**, *4*, 311, and references cited therein.
7. (a) Bonadies, F.; Scarpati, M. L. *Gazz. Chim. Ital.* **1983**, *113*, 421; (b) Amer, A.; Ventura, M.; Zimmer, H. *J. Heterocycl. Chem.* **1983**, *20*, 359; (c) Wiley, R. H.; Kim, K. S. *J. Org. Chem.* **1973**, *38*, 3582; (d) Cocker, W.; Ladwa, P. H.; McMurry, T. B. H.; Ntamila, M. S. *J. Chem. Soc. (C)* **1971**, *9*, 1708; (e) Stacy, G. W.; Cleary, J. W.; Gortatowski, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 1451; (f) Stacy, G. W.; Wagner, G. D. *J. Am. Chem. Soc.* **1952**, *74*, 909.
8. (a) Saalfrank, R. W.; Lutz, T. *Angew. Chem.* **1990**, *102*, 1064; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1041; (b) Saalfrank, R. W.; Lutz, T.; Hoerner, B.; Guendel, J.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1991**, *124*, 2289.
9. (a) Langer, P.; Stoll, M. *Angew. Chem.* **1999**, *111*, 1919; *Angew. Chem., Int. Ed.* **1999**, *38*, 1803; (b) Langer, P.; Schneider, T.; Stoll, M. *Chem. Eur. J.* **2000**, *6*, 3204; (c) Langer, P.; Eckardt, T.; Schneider, T.; Göbel, C.; Herbst-Irmer, R. *J. Org. Chem.* **2001**, *66*, 2222; (d) Ahmed, Z.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3753; for α-hydroxymaleic anhydrides, see: (e) Ullah, E.; Langer, P. *Synlett* **2004**, 2782.
10. For reactions of silyl ketene acetals derived from 3-hydroxyesters, see: (a) Ohtake, H.; Imada, Y.; Murahashi, S.-I. *J. Org. Chem.* **1999**, *64*, 3790; (b) Hattori, K.; Yamamoto, H. *Bioorg. Med. Chem. Lett.* **1993**, *11*, 2337; (c) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099; (d) Caron, B.; Brassard, P. *Tetrahedron* **1993**, *49*, 771; (e) Gu, J. H.; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 1465; (f) Hoffman, R. V.; Kim, H. O. *J. Org. Chem.* **1991**, *56*, 6759; (g) Shirai, F.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6461; (h) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553; (i) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4335.
11. *Typical procedure for the preparation of 1,3-bis(trimethylsilyloxy)alk-1-enes* **2a**–**k**. A THF solution of LDA (50.0 mmol) was prepared by addition of *n*BuLi (20.5 mL, 51.3 mmol, 2.5 M solution in hexanes) to a THF solution (50 mL) of diisopropylamine (5.06 g, 50.0 mmol) at 0 °C. After stirring for 1 h, the solution was cooled to −78 °C and ethyl 3-hydroxyheptanoate (**1f**) (3.92 g, 22.5 mmol) was added. After stirring for 1 h at −78 °C, trimethylchlorosilane (6.11 g, 56.2 mmol) was added and the solution was allowed to warm to 20 °C within 24 h. The solvent and volatile compounds were removed in vacuo and the residue was dissolved in hexane and filtered under inert atmosphere. The filtrate was concentrated in vacuo to give 1-ethoxy-1,3-bis(trimethylsilyloxy)hept-1-ene (**2f**) (7.17 g, 100%) as a clear yellow liquid, which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.37$–4.45 (m, 1H, C*H*CH_2), 3.72 (q, $^3J = 7.1$ Hz, 2H, OCH_2), 3.51 (d, $^3J = 9.0$ Hz, 1H, C*H*$CHCH_2$), 1.20–1.60 (m, 9H, $CH_2CH_2CH_2$, OCH_2CH_3), 0.86–0.94 (m, 3H, $CH_2CH_2CH_3$), 0.23 (s, 9H, $Si(CH_3)_3$), 0.16 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 155.96$ (C), 81.02, 68.60 (CH), 62.81 (OCH_2), 39.29, 28.14, 22.55 (CH_2), 14.32, 14.11 (CH_3), 0.47, 0.31 ($Si(CH_3)_3$); MS (EI, 70 eV): m/z (%) = 317.8 (M^+, 0.15), 260.7 (42), 230.7 (11), 188.7 (13), 146.3 (25), 142.9 (100), 110.0 (19), 102.6 (12), 75.3 (35), 73.5 (77), 55.2 (13), 28.0 (20).
12. *Typical procedure for the preparation of isotetronic acids* **3a**–**k**. To a CH_2Cl_2 solution (10 mL) of **2f** (322 mg, 1.01 mmol) was added a CH_2Cl_2 solution of oxalyl chloride (2 M, 0.505 mL, 1.01 mmol) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C within 16 h. Ether (60 mL) and brine (20 mL) were added, the organic and the aqueous layer were separated and the latter was extracted with ether (3 × 30 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/ether = 1:1) to give **3f** (173 mg, 75%) as slightly orange crystals. IR (KBr, cm^{-1}): $\tilde{\nu} = 3330$ (br, w), 2960 (m), 2935 (m), 2870 (w), 1780 (s), 1708 (s), 1662 (m), 1443 (m), 1378 (w), 1336 (m), 1301 (m), 1226 (m), 1183 (m), 1138 (m) 1103 (m), 1018 (w), 770 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 8.6–7.6 (s, br, 1H, OH), 5.11 (dd, $^3J_1 = 7.9$ Hz, $^3J_2 =$ 2.9 Hz, 1H, CH), 4.30–4.48 (m, 2H, OCH_2), 2.00–2.20 (m, 1H, $CHCH_AH_B$), 1.50–1.70 (m, 1H, $CHCH_AH_B$), 1.45–1.25 (m, 7H, $CH_3CH_2CH_2$), 0.91 (dd, $^3J_1 = {}^3J_2 = 7.1$ Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 165.86$, 164.54, 152.13, 118.71 (C), 78.28 (CH), 61.86 (OCH_2), 32.66, 26.30, 22.20 (CH_2), 14.07, 13.71 (CH_3); MS (EI, 70 eV): m/z (%) = 227.8 (M^+, 3), 182.8 (43), 171.8 (25), 142.9 (100), 125.9 (33), 114.1 (92), 113.1 (89), 96.8 (46), 85.8 (52), 69.8 (71), 41.0 (60), 29.0 (90), 27.9 (47), 27 (47). All products were prepared in racemic form. All products were characterized spectroscopically and gave correct elemental analyses and/or high resolution mass spectra.
13. Nguyen, V. T. H.; Reim, S.; Langer, P. *Tetrahedron Lett.*, in press.
14. Heurtaux, B.; Lion, C.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **2005**, *70*, 1474.