Novel chemoselective tosylation of the alcoholic hydroxyl group of *syn*-α,β-disubstituted β-hydroxy carboxylic acids†

Yikang Wu* and Ya-Ping Sun

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β-Hydroxy acids were readily converted into β-tosyloxy acids (hydroxyl group activation) in moderate to excellent yields *via* the O,O-dianions generated by treatment with methyllithium and thus make it possible to prepare *anti* α,β-disubstituted β-lactones directly from the *syn* aldols.

Activation of hydroxyl groups by converting them into good leaving groups such as tosylate is a very common practice in organic synthesis. However, even such simple transformations can be extremely difficult if other functionalities are present in the molecule. For instance, direct tosylation of the alcoholic OH of unprotected β-hydroxy carboxylic acids has been generally[1a] impossible (although it is known that the thermodecomposition of the cyclic ortho ester derived from a β-monosubstituted β-OH acid and triethyl orthoacetate, led[1b] to the corresponding β-lactone with inversion at the β-carbon, as the minor product in 33% yield along with 42% of an acyclic ester with retained configuration). This is because, under conventional conditions (*e.g.*, TsCl/py/0 °C), tosylation occurs preferentially at the carboxylic OH, with the configuration of the β-carbon (where the hydroxyl group is attached) retained. Although this preference for carboxyl group activation[2] is very useful (it, for instance, underlies the Adams lactonization,[3] essentially the only feasible method for the synthesis of α,β-disubstituted β-lactones from free β-hydroxy acids since the 1970s[4]), it entirely excludes the possibility of all potential transformations based on direct hydroxyl group activation[1] of these acids. Thus, synthesis of *anti*-α,β-disubstituted β-lactones[5] from the corresponding hydroxy acids, for example, must utilize *anti* precursors.

In order to use *syn* aldol products (which are readily accessible through, for example, an Evans/Crimmins aldol reaction,[6] as demonstrated by the enormous number of literature examples, displaying a variety of different substituents at both the α and β positions), a feasible and reliable[7] hydroxyl group activation protocol must be developed first. Herein we wish to show that, by converting the β-hydroxy acids into their O,O-dianions, selectivity of the activation can be totally reversed. A variety of α,β-disubstituted β-hydroxy acids were selectively activated at the hydroxyl group, illustrating a direct approach to the *anti*-α,β-disubstituted β-lactones.

Although O,C-dianions[8] are well-studied, O,O-dianions[9] are only rarely mentioned in the literature. To gain a profile of the deprotonation process, we carried out four parallel experiments, with **1a** as the substrate and 2.5 equiv. of MeLi as the base, at −40 °C in THF for 15, 30, 45, and 120 min respectively, before "quenching" with TsCl. The results showed that 2 h was required for complete dianion formation. At higher temperatures, the deprotonation appeared to be faster (Table 1, entry 1).

The reaction of the O,O-dianions with TsCl, in most cases, was performed at the same temperature as for the deprotonation. To ensure a complete conversion of the dianions into the monotosylates at low temperatures, several-fold excess of TsCl was utilized. The chemoselectivity was excellent (no acyl tosylation product was observed at temperatures up to 5 °C, entry 2).

The length of the chain at the α-carbon did not seem to have much influence on the yields (entries 4 and 7). Introduction of a double bond in the β-chain lowered the yield (entry 8). Presence of an alkoxy group in the α- or β-chain appeared to be beneficial (entries 2, 15, 16). Perhaps a properly located ethereal oxygen somehow stabilized the intermediate dianion through coordination.

An acid without the β-chain was also tosylated in 85% yield (entry 10). However, a substrate without the α-chain failed to afford any expected tosylate under the same conditions (entry 11). Direct attachment of an alkenyl group to the β-carbon also led to full resistance to the tosylation (entry 12). The phenomenon is not understood yet, but the inertness of **1j** is likely to be a consequence of the excessive steric crowding around the hydroxyl group (entry 13).

It is interesting to note that, although with a good leaving group at a liable position, the β-tosyloxy carboxylic acids are reasonably stable after the isolation/purification. Most of them can be stored in a refrigerator for several months without any discernible deterioration (**2a**, however, became **3** after one year).

Preparation of β-lactones appears to be a potential use of **2** with evident significance. Although there were several elegant literature (β-monosubstituted) precedents for forming β-lactones by treating β-mesyloxy acids (not prepared *via* a dianion approach) with a base (such as those reported by Lenz *et al.*,[10a] De Angelis *et al.*,[10b] Bernabei *et al.*,[10c] and Fujisawa *et al.*,[10d] respectively), we suspect that the presence of an additional substituent at the α position, as in our substrates, might cause unexpected difficulty in the lactonization. To exclude this possibility, we also briefly tested conversion of **2** into the corresponding lactones. To our delight, under conditions similar to those reported in the literature,[10] the expected lactones were indeed readily formed in good yields (exemplified in Scheme 2) as reported[10] for the less hindered/less substituted precursors. Besides, the tosylation and the lactonization could also be realized in a one-pot manner‡ in comparable 2-step yields.

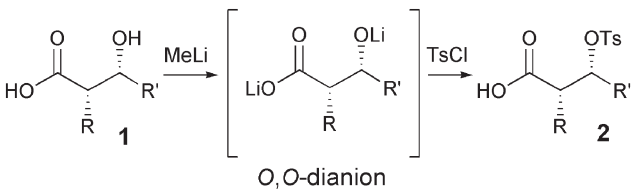
† Electronic supplementary information (ESI) available: listing of physical/spectroscopic data and ^{1}H NMR spectra of all new compounds. See http://www.rsc.org/suppdata/cc/b4/b416383d/

*yikangwu@mail.sioc.ac.cn

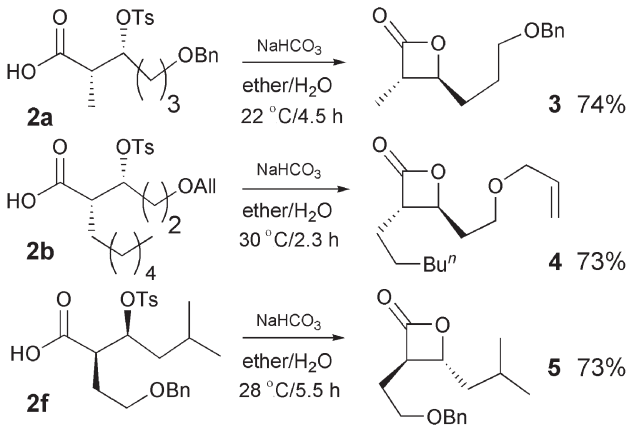
Table 1 Direct hydroxyl group tosylation of **1** (see. Scheme 1 for the general structures and configurations)[a]

Entry	Substrate	R	R′	MeLi[b]	*T* 1[c] (°C)	Time 1[d](h)	TsCl[b]	*T* 2[e] (°C)	Time 2[f] (h)	Product (yield/%)	Recovered substrate (%)
1	**1a**	Me	$(CH_2)_3OBn$	2.2	−10	1.5	4.0	−10	5.0	**2a** (90)	9
2	**1b**	*n*-Hexyl	$(CH_2)_2OCH_2CH{=}CH_2$	2.5	−40	3.0	4.0	0–5	2.0	**2b** (93)	4
3	**1c**	Me	*n*-Pentyl	2.5	−30	2.0	3.0	−30	2.0[g]	**2c** (57)	30
4	**1c**	Me	*n*-Pentyl	3.5	−10	1.5	4.0	−10	1.0	**2c** (78)	20
5[h]	**1d**	*n*-Hexyl	*n*-Pentyl	2.5	−40	2.0	3.0	−40	2.0[i]	**2d** (64)	33
6[h]	**1d**	*n*-Hexyl	*n*-Pentyl	2.5	−30	2.0	3.0	−30	3.0	**2d** (68)	25
7[h]	**1d**	*n*-Hexyl	*n*-Pentyl	3.5	−10	1.5	4.0	−10	1.0	**2d** (81)	14
8	**1e**	Me	$(CH_2)_2CH{=}CH_2$	2.5	−30	2.5	3.0	−30	1.0[j]	**2e** (52)	30
9[h]	**1f**	$(CH_2)_2OBn$	CH_2CHMe_2	3.0	−30	2.0	5.0	−30	3.0	**2f** (87)	8
10	**1g**	*n*-Hexyl	H	2.5	−30	2.0	3.0	−30	1.8[k]	**2g** (85)	11
11[l,m]	**1h**	H	$(CH_2)_2Ph$	3.0	−30	3.0	5.0	−20	2.0	**2h** (0)	−[n]
12[l]	**1i**	Me	(*E*)-CH=CHPh	2.5	−30	3.0	4.0	−30	1.5	**2i** (0)	−[n]
13[h,l]	**1j**	$CHMe_2$	$CHMe_2$	3.0	−30	2.0	5.0	−30	1.5	**2j** (0)	−[n]
14[h]	**1k**	$CH_2CH{=}CH_2$	$(CH_2)_4OCH_2CH{=}CH_2$	2.5	−30	2.0	3.0	−30	1.6[k]	**2k** (66)	29
15	**1l**	*n*-Hexyl	X[o]	2.5	−30	2.0	3.0	−30	2.0	**2l** (86)	12
16	**1m**	*n*-Hexyl	Y[p]	2.5	−30	2.0	3.0	−30	2.0	**2m** (91)	5

[a] For general procedure see the footnote. General procedure for the selective tosylation: to a solution of **1** (1.0 mmol) in THF (2.0 mL) stirred at −78 °C under argon, was added MeLi (2.1 M, 1.05–1.19 mL). The mixture was then stirred at −30 to −40 °C for 2–3 h before a solution of TsCl (3–4 equiv.) in THF (1.0 mL) was added. The stirring was continued at −30 to −40 °C for 2 h. The cooling bath was allowed to warm to 0 °C. 2N HCl (3 mL) was added. The mixture was diluted with EtOAc, washed with water and brine, and dried over Na_2SO_4. Removal of the solvent and chromatography on silica gel (EtOAc–hexanes) gave the pure **2**. [b] Molar equivalents with respect to the substrate. [c] The temperature before introducing TsCl. [d] The reaction time before introducing TsCl. [e] The temperature after introducing TsCl. [f] The reaction time after introducing TsCl. [g] Then stored at −20 °C (freezer) for 8 days. [h] The actual configurations were opposite to those depicted in Scheme 1 (*cf*. **2f** in Scheme 2). [i] Then stored at −20 °C (freezer) overnight. [j] Then at −10 °C for 3 h and at −20 °C (freezer) for 3 days. [k] Then at −20 °C (freezer) for 3 days. [l] Only the starting hydroxy acid was observed on TLC. [m] Racemic **1h** was utilized. [n] Not calculated. [o] X = (*S*)-$(CH_2)CH(OBn)(CH_2)_4Me$. [p] Y = (*S*)-$(CH_2)CH(OBn)(CH_2)_{10}Me$.

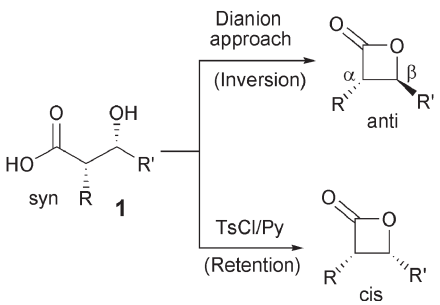


Scheme 1



Scheme 2

In brief, we have conducted a (to our knowledge, the only) systematic study of O,O-dianions and thus added a useful piece to the existing knowledge of dianion chemistry (note that the selectivity observed here may be also applicable to other electrophiles than TsCl). The results disclosed here also illustrate the first feasible general approach to *direct* hydroxyl group activation of α,β-disubstituted β-hydroxy acids and make it possible for the first time to synthesize *anti* α,β-disubstituted β-lactones directly from the readily available β-hydroxy acids. As depicted in Scheme 3, now, just by choosing different reaction conditions (*i.e.*, the conventional TsCl/py or the dianion conditions developed in this work, in combination with the literature[10] lactonization conditions), one can readily realize either inversion or retention at the β position. The methodology developed here should complement existing methods for preparing β-lactones.[4,11]



Scheme 3

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Yikang Wu* and Ya-Ping Sun
State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China.
E-mail: yikangwu@mail.sioc.ac.cn; Fax: +86 (0)21 64166128

Notes and references

‡ This was done by adding Na_2CO_3 (1 mol equiv.) and ether–H_2O (4 mL, 1:1) to the reaction mixture and stirring at 0 °C for 2 h before work-up.

1 (*a*) α-Substituted-*N*-benzoyl-serine (with highly hindered carboxylic but non-hindered alcoholic OH) is the only exception: A. Olma, *Pol. J. Chem.*, 1996, **70**, 1442–1447; (*b*) T. Shiraiwa, M. Suzuki, Y. Sakai, H. Nagasawa, K. Takatani, D. Noshi and K. Yamanashi, *Chem. Pharm. Bull.*, 2002, **50**, 1362–1366.

2 J. Mulzer, G. Bruntrup and A. Chucholowski, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 622–623.

3 W. Adams, J. Baeza and J.-C. Liu, *J. Am. Chem. Soc.*, 1972, **94**, 2000–2006.

4 See, *e.g.*: (*a*) P. Barbier, F. Schneider and U. Widmer, *Helv. Chim. Acta*, 1987, **70**, 1412–1418; (*b*) P. Barbier and F. Schneider, *J. Org. Chem.*, 1988, **53**, 1218–1221; (*c*) Y.-C. Chiang, S. S. Yang, J. V. Heck, J. C. Chabala and M. N. Chang, *J. Org. Chem.*, 1989, **54**, 508–5712; (*d*) N. K. Chadha, A. D. Batcho, P. C. Tang, L. F. Courtney, C. M. Cook, P. M. Wovkulich and M. R. Uskokovic, *J. Org. Chem.*, 1991, **56**, 4714–4718; (*e*) K. Mori and Y. Takahashi, *Liebigs Ann. Chem.*, 1991, 1057–1065; (*f*) P. Wovkulich, K. Shankaran, J. Kiegiel and M. R. Uskokovic, *J. Org. Chem.*, 1993, **58**, 832–839; (*g*) S. Wattanasin, H. D. Do, N. Bhongle and F. G. Kathawala, *J. Org. Chem.*, 1993, **58**, 1610–1612; (*h*) H. Hashizume, H. Ito, T. Morikawa, N. Kanaya, H. Nagashima, H. Usui, H. Tomoda, T. Sunazuka, H. Kumagai and S. Omura, *Chem. Pharm. Bull.*, 1994, **42**, 2097–2107; (*i*) H. Tomoda, H. Kumagai, Y. Ogawa, T. Sunazuka, H. Hashizume, H. Nagashima and S. Omura, *J. Org. Chem.*, 1997, **62**, 2161–2165; (*j*) O. Dirat, C. Kouklovsky and Y. Langlois, *J. Org. Chem.*, 1998, **63**, 6634–6642; (*k*) A. K. Ghosh and S. Fidanze, *Org. Lett.*, 2000, **2**, 2405–2407; (*l*) A. K. Mandal, *Org. Lett.*, 2002, **4**, 2043–2045.

5 See, *e.g.*: (*a*) D. C. Alridge, D. Giles and W. B. Turner, *J. Chem. Soc. D*, 1970, 639–639; (*b*) S. Kondo, K. Uotani, M. Miyamoto, T. Hazato, H. Naganawa and T. Aoyagi, *J. Antibiot.*, 1978, **31**, 797–800; (*c*) K. Yoshinari, M. Aoki, T. Ohtsuka, N. Nakayama, Y. Itezono, M. Mutoh, J. Watanabe and K. Yokose, *J. Antibiot.*, 1994, **47**, 1376–1384; (*d*) E. Hochuli, E. Kupfer, R. Maurer, W. Meister, Y. Mercadal and K. Schmidt, *J. Antibiot.*, 1987, **40**, 1086–1091.

6 See, *e.g.*: (*a*) D. A. Evans, *Science*, 1988, **240**, 420–426; (*b*) M. T. Crimmins, B. W. King, E. A. Tabet and K. Chaudhary, *J. Org. Chem.*, 2001, **66**, 894–902. Note that the absolute configurations of the newly formed chiral centers in the aldols are predictable in almost all cases and a great many different substituents at the α and β carbons have been reported in the literature over the last few decades.

7 For example, the Mitsunobu reaction, which is well-known for configuration inversion at the hydroxyl carbon in the synthesis of lactones, does not always lead to inversion. See: (*a*) C. Ahn and P. DeShong, *J. Org. Chem.*, 2002, **67**, 1754–1759. Note also that the Mitsunobu reaction is only rarely applicable to the synthesis of β-lactones (β-unsubstituted/unhindered at the alcoholic OH). See: (*b*) A. E. Ramer, R. N. Moore and J. C. Vederas, *Can. J. Chem.*, 1986, **64**, 706–713.

8 See, *e.g.*: P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, Jr., *J. Org. Chem.*, 1972, **37**, 451–458.

9 Methylation/benzylation (not specified but presumably *via* O,O-dianion employing NaH/DMF/rt conditions) of serine or threonine is known. See, *e.g.*: (*a*) Y. Nihiyama, S. Shikama, K.-I. Morita and K. Kurita, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1949–1954; (*b*) M. Taniguchi, K.-I. Suzumura, K. Nagai, T. Kawasaki, T. Saito, J. Takasaki, K.-I. Suzuki, S. Fujita and S.-I. Tsukamoto, *Tetrahedron*, 2003, **59**, 4533–4538. However, such conditions completely failed to give any **2** when applied to **1** (presumably because the OTs, as in our substrates, is a much better leaving group than OMe or OBn, as in the literature cases, and thus more liable to various side reactions under the literature conditions).

10 (*a*) Y. Zhang, R. A. Gross and R. W. Lenz, *Macromolecules*, 1990, **23**, 3206–3212; (*b*) F. De Angelis, E. De Fusco, P. Desiderio, F. Giannessi, F. Piccirilli and M. O. Tinti, *Eur. J. Org. Chem.*, 1999, 2705–2707; (*c*) I. Bernabei, R. Castagnani, F. De Angelis, E. De Fusco, F. Giannessi, D. Misiti, S. Muck, N. Scafetta and M. O. Tinti, *Chem. Eur. J.*, 1996, **2**, 826–831; (*d*) T. Sato, T. Kawara, A. Nishizawa and T. Fujisawa, *Tetrahedron Lett.*, 1980, **21**, 3377–3380.

11 For pre-1999 reports on the synthesis of β-lactones in general, see an excellent review: (*a*) H. W. Yang and D. Romo, *Tetrahedron*, 1999, **55**, 6403–6434. For more recent reports, see *e.g.*: (*b*) Y.-C. Wang, C.-X. Zhao and D. Romo, *Org. Lett.*, 1999, **1**, 1197–1199.

12 C. Weller, B. Costisella and H. Schick, *J. Org. Chem.*, 1999, **64**, 5301–5303.

13 K. Castle, C.-S. Hau, J. B. Sweeney and C. Tindall, *Org. Lett.*, 2003, **5**, 757–759.

14 S. G. Nelson, T. J. Peelen and Z. Wan, *J. Am. Chem. Soc.*, 1999, **121**, 9742–9743.

15 S. G. Nelson and Z. Wan, *Org. Lett.*, 2000, **2**, 1883–1886.

16 C. Zhu, X. Shen and S. G. Nelson, *J. Am. Chem. Soc.*, 2004, **126**, 5352–5353.

17 O. V. Larionov and A. de Meijere, *Org. Lett.*, 2004, **6**, 2153–2156.