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Diethyl oxomalonate as a three carbon synthon for synthesis of functionalized 1,1′-disubstituted tetrahydroisoquinoline

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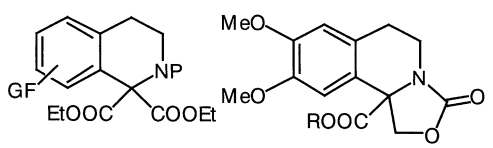
Abstract—Pictet–Spengler condensation of β-arylethylamine with diethyl oxomalonate provides an entry to highly functionalized 1,1′-disubstituted tetrahydroisoquinoline in high yield. Selective functionalization of two ester groups is demonstrated. © 2001 Elsevier Science Ltd. All rights reserved.

Generation of a quaternary carbon center is a non-trivial exercise even in today's standard and represents a challenging and dynamic area in organic synthesis.[1] 1,1′-Disubstituted tetrahydroisoquinolines, a particular structure of this group, have been found within the structure of a number of natural products such as cactus alkaloids,[2] spirobenzylisoquinoline alkaloids,[3] Erythrina family alkaloids[4] and the ecteinascidine series.[5] From the stand point of synthesis, the sequential alkylation of a suitably activated parent tetrahydroisoquinoline[6] and the classic Pictet–Spengler reaction[7] are the most obvious way for their construction. While aldehydes participate well in the Pictet–Spengler reaction, ketones are far less reactive. Indeed, only activated ketone carbonyl groups[8–10] react efficiently with electron-rich β-phenylethylamines to provide the title compound. Interestingly, the readily available diethyl oxomalonate[11] has rarely been employed as an electrophile in such a reaction,[12] in spite of its potential to offer highly functionalized 1,1′-disubstituted tetrahydroisoquinoline that is amenable to further chemical manipulations. In connection with our ongoing project, we had occasion to examine this reaction and wish to report in this letter our preliminary results on the synthesis of compounds **1** and its subsequent transformation to **2**, a constrained serine analogue (Fig. 1).[13]

After a brief survey of reaction conditions varying the solvent (benzene, dioxane, toluene), the acid (AcOH, TFA, ytterbium triflate) and the temperature, it was found that the desired compound **1a** can be obtained in 96% yield by simply heating a solution of β-(3,4-dimethoxy)phenylethylamine **4** and diethyl oxomalonate in toluene–TFA (v/v = 99/1) to 85°C for 3 h. Decarboxylation leading to ethyl tetrahydroisoquinoline-1-carboxylate was found to be the major side product in other conditions investigated. Table 1 lists the results of the condensation reaction of diethyl oxomalonate with various β-arylethylamines. As is seen, tetrahydroisoquinolines were obtained in all cases with excellent yields. In accord with the normal regioselectivity pattern of a Pictet–Spengler reaction, two regioisomers **1b** and **1c** were produced from the β-(3,4-dimethoxy-5-isopropyloxy)phenylethylamine **5** (entry 2). On the other hand, a single regioisomer **1d** was isolated from the closely related 3-demethylmescaline **6** (entry 3). Apparently for both steric and stereoelectronic reasons, the cyclization occurred exclusively at the position *ortho* to the free hydroxy function. Dopamine **9** and its methyl ester **10** participated in this reaction with equal efficiency. The *N*-Boc amino alcohol **11** can be engaged directly in this reaction, leading to the *N*-deprotected compound **1i**, without the concomitant occurrence of lactonization. Due to the high



1 **2** R = H, **3** R = Me

Figure 1.

Keywords: 1,1′-disubstituted tetrahydroisoquinoline; Pictet–Spengler reaction; diethyl oxomalonate; quaternary carbon; conformationally constrained amino acid.

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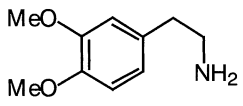
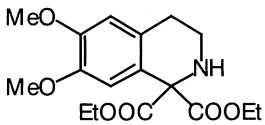
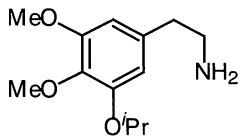
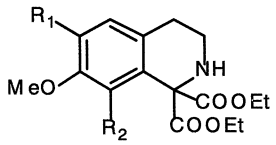
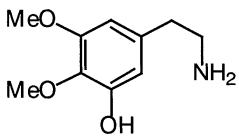
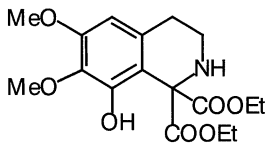
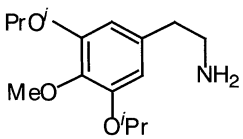
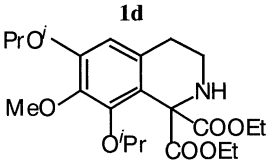
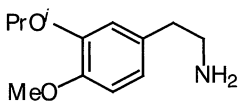
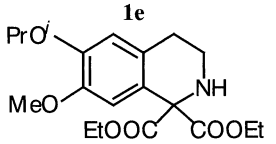
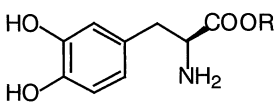
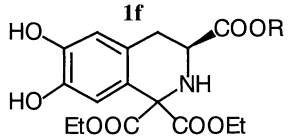
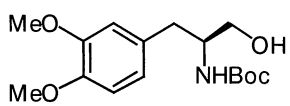
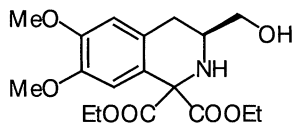
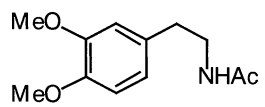
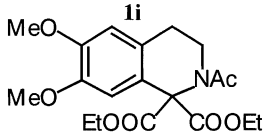
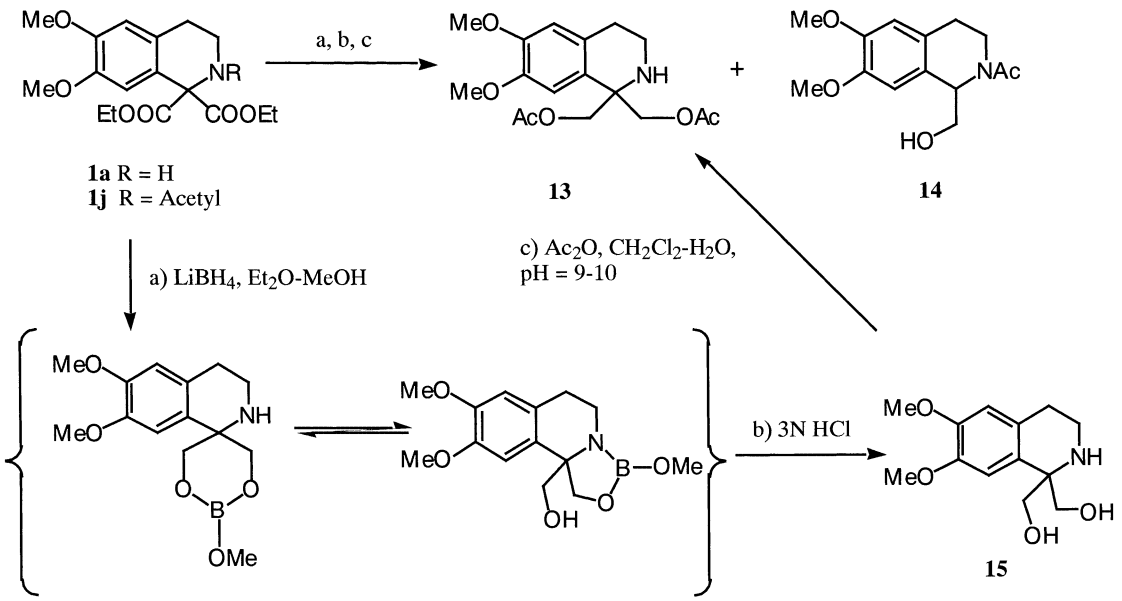
Table 1. Synthesis of 1,1-diethoxycarbonyl tetrahydroisoquinoline

Entries	Amines	Reaction time	Products	Isolated yield (%)
1	 **4**	2h	 **1a**	96
2	 **5**	5h	 **1b** $R_1 = O^iPr$, $R_2 = OMe$ **1c** $R_1 = OMe$, $R_2 = O^iPr$	85 **1b/1c** = 3/2
3	 **6**	2h	 **1d**	85
4	 **7**	4h	 **1e**	98
5	 **8**	4h	 **1f**	90
6	 **9** R = H **10** R = Me	2h	 **1g** R = H **1h** R = Me	R = H, 98 R = Me, 98
7	 **11**	2h	 **1i**	95
8	 **12**	2h	 **1j**	96

electrophilicity of the diethyl oxomalonate, its reaction with *N*-acyl arylethylamine **12** occurred smoothly to provide the *N*-acetyl tetrahydroisoquinoline **1j** in 96% yield.

We next turned our attention to the selective functionalization of tetrahydroisoquinoline. Selective saponification of one ester function was complicated by the concomitant decarboxylation and efforts were thus oriented toward the reduction process. After a screening of different reducing agents including LAH, DIBAL-H, L-Selectride, $LiAl(OMe)_3H$, $LiAl(O^tBu)_3H$,[14] it was found that reduction of **1a** with $LiBH_4$ gave reproducibly the amino diol, which, after acidic treatment,

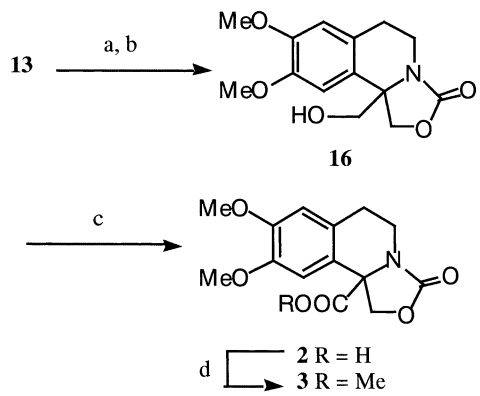


Scheme 1.

was directly acetylated under Schotten–Baumann conditions to provide the corresponding diacetate **13** in 65% overall yield (Scheme 1).[15] 1-Hydroxymethyl *N*-acetyl-tetrahydroisoquinoline **14** was isolated as a side-product, which accounts for the overall mass-balance. The expulsion of the ester function assisted by the nitrogen lone pair under these reduction conditions or the retro-aldolization of intermediate β-hydroxy ester could explain its formation. Isolation of diacetate **13** under the classic Schotten–Baumann conditions was surprising at the first glance, since these conditions are known to selectively acylate the amine in the presence of an alcohol function. We speculated that the 1,1-disubstitution pattern might be responsible for this observation. Indeed, acylation of the amine would unavoidably introduce a severe allylic 1,3-strain[16] because of the presence of a pseudo-equatorial substitutent at the C-1 position. The fact that normal chemoselectivity pattern was re-installed in the formation of compound **14** is supportive of the above hypothesis. Applying the same reduction–hydrolysis–acylation sequence to the *N*-acylated derivative **1j** provided a very similar result. It is appropriate to point out that the amino diol **15** was soluble in water and that acylation facilitates the purification process.

While desymmetrization of diacetate **13** will potentially provide the optically active material,[17] we focused our efforts on the functional group manipulation of **13** at this stage of development. Thus, aminolysis of **13** (gaseous NH_3 in MeOH) followed by treatment with triphosgene provided the oxazolidinone **16** in 60% yield. Oxidation of the primary alcohol (TEMPO–NaClO) furnished the carboxylic acid **2** in quantitative yield that was fully characterized as its corresponding methyl ester **3** (Scheme 2). These two compounds are immediate precursors of cycle C of ecteinascidine-743 and could also be considered as a conformationally biased serine analogue. An asymmetric synthesis of regioisomeric 3-hydroxymethyl tetrahydroisoquinoline-3-carboxylic acid has recently been reported from the group of Bonin, Micouin, and Husson.[18]

In conclusion, we have described a facile synthesis of functionalized 1,1-disubstituted tetrahydroisoquinoline from easily accessible starting materials. Such compounds could be useful building blocks in complex natural product syntheses, as well as in design of the conformationally constrained peptidomimetics.



Scheme 2. (a) NH_3 in MeOH; (b) triphosgene, Et_3N, CH_2Cl_2, 60% for two steps; (c) TEMPO, NaClO, acetone, $NaHCO_3$ aq.; (d) $SOCl_2$, MeOH, 98% for two steps.

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References

1. (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401; (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066; (c) D'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505; (d) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460.
2. Lundström, J. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, NY, 1983; Vol. 21, pp. 255–327.
3. Blaskó, G. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, NY, 1990; Vol. 38, pp. 157–224.
4. Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, NY, 1996; Vol. 48, pp. 249–337.
5. (a) Rinehart, K. L. *Med. Res. Rev.* **2000**, *20*, 1–27; (b) For a total synthesis, see: Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.
6. (a) Meyers, A. I.; Du, B.; Gonzalez, M. A. *J. Org. Chem.* **1990**, *55*, 4218–4220; (b) Meyers, A. I.; Gonzalez, M. A.; Struzka, V.; Akahane, A.; Guiles, J.; Warmus, J. S. *Tetrahedron Lett.* **1991**, *32*, 5501–5504; (c) Meyers, A. I.; Akahane, A.; Struzka, V.; Warmus, J. S.; Gonzalez, M. A.; Milot, G. *Tetrahedron Lett.* **1997**, *38*, 4195–4198.
7. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
8. Keto acids, see: (a) Hudlicky, T.; Kutchan, T. M.; Shen, G.; Sutliff, V. E.; Coscia, C. J. *J. Org. Chem.* **1981**, *46*, 1738–1741; (b) Chrzanowska, M.; Schönenberger, B.; Brossi, A.; Flippen-Anderson, J. L. *Helv. Chim. Acta* **1987**, *70*, 1721–1731; (c) Sekine, Y.; Creveling, C.; Bell, M.; Brossi, A. *Helv. Chim. Acta* **1990**, *73*, 426–432; (d) Irikawa, H.; Ooe, S.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3365–3367; (e) Kawai, M.; Deng, Y. L.; Kimura, I.; Yamamura, H.; Araki, S.; Naoi, M. *Tetrahedron: Asymmetry* **1997**, *8*, 1487–1490.
9. Vicinal dicarbonyl and tricarbonyl, see: Venkov, A. P.; Lukanov, L. K. *Synth. Commun.* **1996**, *26*, 755–762.
10. Vicinal vinyl tricarbonyl, see: (a) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371–372; (b) Wasserman, H. H.; Amici, R. M. *J. Org. Chem.* **1989**, *54*, 5843–5844.
11. Commercially available from Aldrich. For syntheses, see: (a) Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891–892; (b) Tietz, L. F.; Bratz, M. *Org. Syn*; John Wiley & Sons: New York, NY, 1993; Vol. 71, pp. 214–219; (c) Wasserman, H. H.; Lee, K.; Xia, M. *Tetrahedron Lett.* **2000**, *41*, 2511–2514 and references cited therein.
12. Condensation of tryptamine-2-carboxylic acid with diethyl oxomalonate has been reported by Cook et al., see: (a) Narayanan, K.; Cook, J. M. *Tetrahedron Lett.* **1990**, *31*, 3397–3400; (b) Narayanan, K.; Schindler, L.; Cook, J. M. *J. Org. Chem.* **1991**, *56*, 359–365; For Fridel–Crafts reaction, see: (c) Ghosh, S.; Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1982**, *47*, 4692–4702; For aza-ene reaction, see: (d) Tietz, L. F.; Bratz, M. *Chem. Ber.* **1989**, *122*, 997–1002.
13. (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267; (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699–1720; (c) Review on the synthesis of α,α-disubstituted amino acids, see: Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
14. For recent selective reduction of α,α′-dialkylated malonate, see: (a) Davis, C. R.; Swenson, D. C.; Burton, D. J. *J. Org. Chem.* **1993**, *58*, 6843–6850; (b) Ayers, T. A. *Tetrahedron Lett.* **1999**, *40*, 5467–5470.
15. Physical data of **13**: IR ($CHCl_3$) ν 1740, 1516, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 6H), 2.45 (br s, 1H, NH), 2.74 (t, $J=6.0$ Hz, 2H); 3.11 (t, $J=6.0$ Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.25, 4.34 (AB system, $J=12.0$ Hz, 4H), 6.6 (s, 1H), 6.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.9, 29.7, 38.6, 55.7, 56.0, 56.9, 67.2, 109.3, 112.0, 128.9, 126.4, 147.1, 148.1, 170.6; MS (ESI) m/z 360 $(M+Na)^+$, 338 $(M+1)^+$.
16. Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860 and references cited therein.
17. For a review, see: Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769–3826.
18. Alezra, V.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2001**, *42*, 2111–2113.