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Linchpin Construction of Unsymmetrical 1,4-Alkynediols

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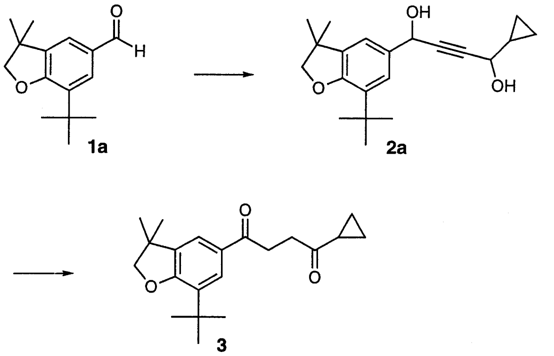
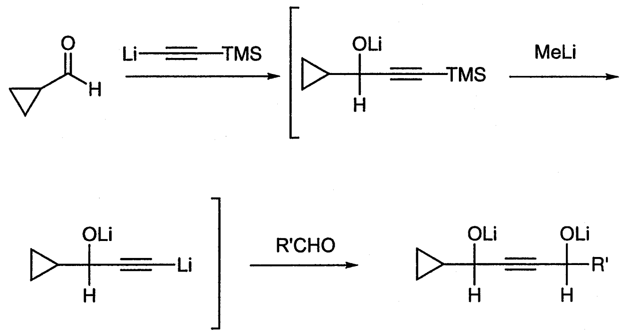
Abstract: A one-pot preparation of unsymmetrical 1,4-alkynediols such as **2a** by the coupling of trimethylsilylacetylene and two different aldehydes or ketones is reported. The dilithiated species **5** is generated by the sequential addition of the first aldehyde or ketone **1b** to a solution of lithium trimethylsilylacetylide, followed by the addition of methyllithium, which removes the trimethylsilyl protecting group. Addition of the second aldehyde or ketone then leads to the unsymmetrical 1,4-alkynediol **2a**.

In the course of other work, we needed to prepare the diketone **3**, a metabolite of a potent nonsteroidal antiinflammatory agent.[1] We thought that **3** could easily be prepared from the corresponding 1,4-alkynediol **2a**. We report a simple one-pot procedure for the preparation of such unsymmetrical 1,4-alkynediols.



Although several approaches had been described for the preparation of symmetrical and unsymmetrical 1,4-alkynediols,[2–4] remarkably, none allowed a simple linchpin coupling of two different aldehydes or ketones. It seemed possible (Scheme 1) that the necessary three-chemical-step sequence, addition of lithium trimethylsilylacetylide to the first aldehyde, desilylation[5] to the dilithio intermediate with CH_3Li, and addition of the second aldehyde or ketone, could be carried out without intervening workup. The success of this strategy now allows the convenient one-pot preparation of unsymmetrical 1,4-alkynediols such as **2a**.

SCHEME 1



Aldehydes, ketones, α,β-unsaturated aldehydes, and even some heterocylic carboxaldehydes have been used successfully (Table 1). It is important that the order of addition of the two electrophiles is done with regard to their complexity and reactivity toward MeLi. For example, *m*-anisaldehyde **1f** (Table 1, entry 4) could not be used as the first aldehyde, since ortho metalation of the aromatic ring by methyllithium competed with the removal of the trimethylsilyl group. When aldehyde **1a**[1] was used first (Table 1, entry 1), the yield of 1,4-alkynediol **2a** was only 31%, whereas when cyclopropanecarboxaldehyde **1b** was used first (Table 1, entry 2), the yield increased to 61%. The use of 2 equiv of cyclopropanecarboxaldehyde (Table 1, entry 3) led to a modest further increase in yield. It should also be noted that when a ketone is used as the first electrophile (Table 1, entry 7), the desilylation by MeLi seemed to occur more slowly. The careful titration of *n*-BuLi and the MeLi prior to use is crucial to avoid side reactions, and the reaction must be run in tetrahydrofuran, since the deprotection of the trimethylsilyl group did not occur in diethyl ether. Except for entry 5, which is symmetrical, the reaction proceeds to give (^{13}C NMR) a ∼1:1 mixture of diastereomers. This method could be particularly useful when the intermediate propargyl alcohol (e.g the alcohol derived from cyclopropanecarboxaldehyde, Scheme 1) is not commercially available.

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(2) For leading references to the preparation of racemic unsymmetrical 1,4-alkynediols by the addition of propargylic alcohols to aldehydes or ketones, see: (a) Saimoto, H.; Kusano, Y.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 1607−1610. (b) Uchida, S.; Yokoyama, Y.; Kiji, J.; Okano, T.; Kitamura, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2961−2967. (c) van Boxtel, L. J.; Korbe, S.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, *12*, 2283−2292. Other routes to racemic unsymmetrical 1,4-alkynediols include the following: (d) From 1-chloroalkyl *p*-tolylsulfoxide: Satoh, T.; Hayashi, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2153-2158. (e) From propynal and organometallics: Priebe, H.; Hopf, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 286. (f) From propynal and methyl diazoacetate: Margorskaya, O. I.; Medvedeva, A. S.; Demina, M. M.; Kalikhman, I. D.; Voronkov, M. G. *J. Organomet. Chem.* **1989**, *376*, 31−40. (g) By mono or bis oxidation of propargylic methylenes with SeO_2: Chabaud, B.; Sharpless, B. K. *J. Org. Chem.* **1979**, *44*, 4202−4203.

(3) For the stereoselective synthesis of unsymmetrical 1,4-alkynediols, see the following: (a) By a [2,3] Wittig rearrangement of a propargylic allylic ether: Marshall, J. A.; Jenson, T. M.; DeHoff, B. S. *J. Org. Chem.* **1987**, *52*, 3860−3866. (b) From the zinc triflate mediated addition of a propargylic alcohol to an aldehyde: Boyall, D.; Lopez, F.; Sasaki, H.; Frantz, D.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233−4236. (c) From a 1-chloroalkyl epoxide precursor: Li, W.-D.; Li, Y.-L.; Li, Y. *J. Chin. Chem. Soc.* **1995**, *42*, 701−708.

(4) For a diastereoselective synthesis of unsymmetrical 1,4-alkynediols by the Lewis acid mediated addition of a metal acetylide to an acetal, see Yamamoto, Y.; Abe, H.; Nishii, S.; Yamada, J−i. *J. Chem. Soc., Perkin Trans.* 1 **1991**, 3253.

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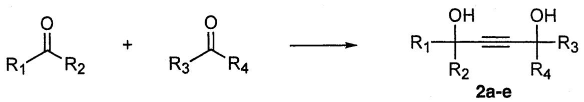
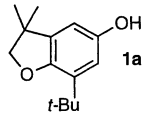
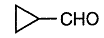
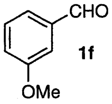
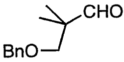
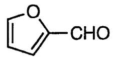
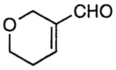
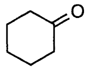
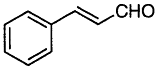
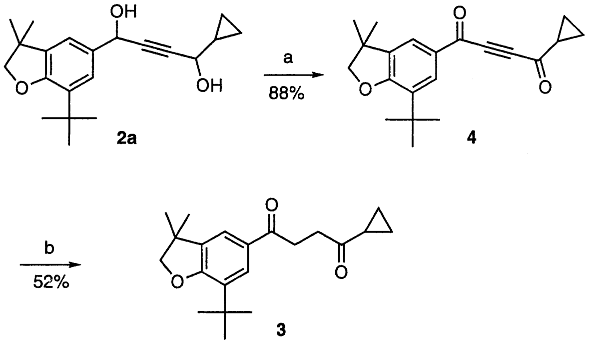
TABLE 1. Coupling of Two Aldehydes and/or Ketones To Prepare the Corresponding Alkyne-1,4-diols



entry	electrophile 1	electrophile 2[a]	Yield (%)[b]
1	 **1a**	 **1b**	31 (**2a**)
2	**1b**	**1a**	61 (**2a**)
3	**1b**	**1a**	65 (**2a**)[c]
4	$C_5H_{11}CHO$ **1c**	 **1f**	69 (**2b**)
5	 **1d**	 **1g**	66 (**2c**)
6	**1b**	 **1h**	68 (**2d**)
7	 **1e**	 **1j**	52 (**2e**)

[a] 1.3 equiv was used. [b] Figures refer to isolated yields (calcd from component no. 1), after flash chromatography and are unoptimized. [c] 2.0 equiv of **1b** was used, and the yield is based on the amount of **1a**.

SCHEME 2[a]



[a] Conditions: (a) Jones' reagent, acetone, rt; (b) Pd/$BaSO_4$, hexanes, H_2, rt.

With **2a** in hand, the synthesis of the metabolite **3** was straightforward (Scheme 2). As the Pd-mediated isomerization[6] of the alkynediol to the 1,4-diketone failed, we opted for a two-step procedure, first oxidizing[7] the diol to the corresponding diketone, then effecting the catalytic reduction of the triple bond. With 5% Pd/C in MeOH, overreduction of the benzylic ketone occurred too rapidly to be avoided, but with 5% Pd/$BaSO_4$ in hexanes only the triple bond was reduced. As expected, the 1,4-diketone **3** was unstable, but it could be isolated pure after chromatography and crystallization from cold hexanes.

We have shown that unsymmetrical 1,4-alkynediols can be efficiently prepared from two different aldehydes or ketones in a one-pot procedure. We expect that the simple procedure described here for the assembly of unsymmetrical 1,4-diketones, valuable intermediates for the synthesis of furans, pyrroles, and cyclopentenones, will also be useful.

Experimental Section

General. ^1H NMR and ^{13}C NMR were measured at 250 MHz for ^1H and 62.5 MHz for ^{13}C in $CDCl_3$. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils unless specified otherwise. Low- and high-resolution mass spectra were measured at 70 eV. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Substances for which C, H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 cm × 10 cm ×250 mm analytical plates coated with silica gel GF, developed in the solvent system indicated. Flash chromatography was performed as described by Still[8] using silica gel 60 (230−400 mesh). Solvents are referred to as volume/volume mixtures. All air- and moisture sensitive reactions were performed in oven-dried glassware under a positive pressure of nitrogen. All solvents were purified immediately prior to use. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl under dry nitrogen. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 under dry nitrogen. All reaction mixtures were stirred magnetically under a nitrogen atmosphere. *n*-Butyllithium and methyllithium were titrated before use. Commercially available aldehydes and aldehyde **1e** were purified by distillation prior to use. Aldehyde **1a** was purified by chromatography and dried under reduced pressure for 12 h before use. Trimethylsilylacetylene was purchased from Aldrich and used without further purification. The diols prepared using this method are a 1:1 mixture of diastereoisomers.

Compound 2a. *n*-BuLi (2.2 M in hexanes, 1.85 mL, 4.07 mmol) was added at −78 °C over 5 min to a stirred solution of trimethylsilylacetylene (610 μL, 4.32 mmol) in THF (21.5 mL). After 5 min at −78 °C, the bath was removed and the solution was stirred for another 20 min before again being cooled to −78 °C. Cyclopropanecarboxaldehyde (320 μL, 4.28 mmol) in THF (2 mL + 1 mL rinse) was added and the mixture was stirred for 10 min at −78 °C, then 2 h at room temperature. The mixture was chilled to −78 °C, then MeLi (1.45 M in ether, 3.0 mL, 4.31 mmol) was added. The pale yellow mixture was stirred for 10 min at −78 °C, then 3 h at room temperature. The mixture was chilled to −78 °C, aldehyde **1a** (501 mg, 2.16 mmol) in THF (2 mL + 1 mL rinse) was added, and the mixture was stirred for 30 min before being warmed to room temperature overnight. The reaction mixture was partitioned between ethyl acetate (50 mL) and, sequentially, 20% saturated aqueous NH_4Cl (20 mL) and brine (50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield **2a** (457 mg, 65% yield from **1a**) as a pale yellow oil. TLC R_f 0.32 (petroleum ether−ethyl acetate, 7:3); ^1H NMR δ 0.45−0.60 (m, 4H), 1.24 (m, 1H), 1.32, (s, 6H), 1.35 (s, 9H), 2.45 (br s, 1H), 4.23, (s, 2H), 4.32 (m, 1H), 5.42 (m, 1H), 7.14 (d, 1H, J = 1.75 Hz), 7.23 (d, 1H, J = 1.25 Hz); ^{13}C NMR δ u 157.4, 137.5, 133.1, 132.5, 132.5, 85.5, 85.4, 85.3, 84.2, 41.6, 34.3, 3.5,

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(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

1.8; ^{3}C NMR δ d 124.1, 118.8, 65.7, 64.8, 64.7, 29.4, 27.6, 17.1; IR (film) 3331, 2957, 2870 cm^{-1}; MS (CI, 70 eV) *m*/*z* 217 (100), 233 (92) 295 (21), 311 (30), 328 (M^{+}, 21); HRMS calcd for $C_{21}H_{28}O_3$ (M^{+}) 328.2038, found 328.2040.

Compound 2b. The same procedure was followed starting from hexanal (503 mg, 5.0 mmol) and *m*-anisaldehyde (790 μL, 6.5 mmol), yielding **2b** (911 mg, 69% yield from **1c**) as a pale yellow oil that crystallized on standing. TLC R_f 0.31 (petroleum ether−ethyl acetate, 7:3); ^{1}H NMR δ 0.87 (app. t, 3H), 1.20−1.73 (m, 8H), 3.06 (br s, 1H), 3.53 (br s, 1H), 3.78 (s, 3H), 4.38 (app. t, 1H, $J = 6.62$ Hz), 5.42 (app. d, 1H, $J = 6.62$ Hz), 6.83 (d, 1H, $J = 8.25$ Hz), 7.08 (m, 2H), 7.26 (t, 1H, $J = 8$ Hz); ^{13}C NMR δ u 159.7, 142.2, 87.9, 84.6, 37.7, 31.6, 25.1, 22.7; ^{13}C NMR δ d 129.7, 119.1, 114.0, 112.3, 64.4, 64.3, 62.6, 62.5, 55.4, 14.2; IR (KBr) 3246, 2934, 2857, 1602 cm^{-1}; MS (CI, 70 eV) *m*/*z* 135 (100) 245 (45) 262 (M^{+}, 80); HRMS calcd for $C_{16}H_{22}O_3$ (M^{+}) 262.1568, found 262.1565. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46. Found: 73.02; H, 8.72.

Compound 2c. The same procedure was followed starting from aldehyde **1d**[9] (498 mg, 2.58 mmol) and furfural (280 μL, 3.38 mmol), yielding **2c** (540 mg, 66% yield from **1c**) as a pale yellow oil. TLC R_f 0.37 (petroleum ether−ethyl acetate, 7:3); ^{1}H NMR δ 0.98 (s, 3H), 1.10 (s, 3H), 2.65 (br s, 1H), 3.27 (d, 1H, $J = 8.75$ Hz), 3.63 (dd, 1H, $J = 8.75$, 2.50 Hz), 3.65 (br s, 1H), 4.29 (app. s, 1H), 4.50 (app. s 2H), 5.47, (s, 1H), 6.33 (m, 1H), 6.42 (m, 1H), 7.32 (m, 5H), 7.39 (m, 1H); ^{13}C NMR δ u 153.2, 143.0, 137.9, 85.5, 83.1, 78.0, 73.8; 39.4; ^{13}C NMR δ d 128.6, 127.9, 127.8, 110.5, 107.9, 70.5, 58.2, 58.3, 22.6, 22.3, 21.3; IR (film) 3391, 2965, 2870 cm^{-1}; MS (CI, 70 eV) *m*/*z* 91 (100), 297 ((M − OH)$^{+}$, 18), 313 ((M − H)$^{+}$, 2); HRMS calcd for $C_{19}H_{22}O_4$ (M − H^{+}) 313.1439, found 313.1432. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.57; H, 7.06. Found: 72.32; H, 7.20.

Compound 2d. The same procedure was followed starting from cyclopropanecarboxaldehyde (320 μL, 4.28 mmol) and aldehyde **1h** (620 mg, 5.52 mmol), yielding **2d** (607 mg, 68% yield from **1b**) as a pale yellow oil. TLC R_f 0.22 (petroleum ether−ethyl acetate, 1:1); ^{1}H NMR δ 0.38−0.59 (m, 4H), 1.24 (m, 1H), 2.19 (m, 2H), 3.49−3.69 (m, 2H), 3.77 (t, 2H, $J = 5.75$ Hz), 4.2−4.4 (m, 3H), 4.81 (s, 1H), 6.02 (s, 1H); ^{13}C NMR δ u 136.3, 85.6, 83.2, 65.1, 64.3, 25.1, 3.5, 1.9; ^{13}C NMR δ d 122.0, 65.7, 63.6, 17.2; IR (film) 3356, 2854 cm^{-1}; MS (CI, 70 eV) *m*/*z* 83 (100), 191.1 (28) 207 (M^{+}, 5); HRMS calcd for $C_{12}H_{16}O_3$ (M^{+}) 207.1021, found 207.1016.

Compound 2e. The same procedure was followed starting from cyclohexanone (497 mg, 5.06 mmol) and *trans*-cinnamaldehyde (836 mg, 6.32 mmol), yielding **2e** (680 mg, 52% yield from **1e**) as a pale yellow oil that crystallized on standing. TLC R_f 0.26 (petroleum ether−ethyl acetate, 7:3); ^{1}H NMR δ 1.21−1.98 (m, 10H), 2.98 (br s, 1H), 3.16 (br s, 1H), 5.10 (d, 1H, $J = 5.5$ Hz), 6.29 (dd, 1H, $J = 15.75$, 5.75 Hz), 6.75 (d, 1H, $J = 15.75$ Hz), 7.3 (m, 5H); ^{13}C NMR δ u 136.3, 136.2, 90.4, 83.3, 83.4, 68.9, 40.0, 25.3, 23.5; ^{13}C NMR δ d 132.0, 128.8, 128.3, 127.0, 63.0; IR (KBr) 3276, 2935, 2857 cm^{-1}; MS (CI, 70 eV) *m*/*z* 141 (100), 223 (62), 239 (56), 256 (M^{+}, 10); HRMS calcd for $C_{17}H_{20}O_2$ (M^{+}) 256.1463, found 256.1458. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.64; H, 7.87. Found: 79.54; H, 7.79.

Compound 6. Jones' reagent (5.1 mL, 6.84 mmol) was added to an ice-cooled solution of **2a** (850 mg, 2.59 mmol) in acetone (26 mL). The mixture was stirred for 30 min, then MeOH (20 mL) was added. After 10 min, the reaction mixture was partitioned between ethyl acetate (50 mL) and, sequentially, water (200 mL) and brine (50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to yield **6** as a yellow oil (750 mg, 88% yield from **2a**). TLC R_f 0.43 (petroleum ether−ethyl acetate, 9:1); ^{1}H NMR δ 1.17 (m, 4H), 1.37 (s, 6H), 1.38 (s, 9H), 2.04 (m, 1H), 4.37 (s, 2H), 7.72 (d, 1H, $J = 1.46$ Hz), 7.91 (d, 1H, $J = 1.46$ Hz); ^{13}C NMR δ u 187.0, 175.2, 163.9, 138.6, 133.8, 129.6, 85.3, 84.7, 84.4, 41.1, 34.4, 11.9; ^{13}C NMR δ d 129.2, 122.4, 29.1, 27.7, 25.0; IR (film) 2960, 1667, 1643 cm^{-1}; MS (NH_3 − CI, 70 eV) *m*/*z* 231.2 (100), 309.2 (38), 325.2 (32); HRMS calcd for $C_{21}H_{24}O_3$ (M^{+}) 324.1725, found 324.1723.

Compound 3. Diketone **6** (810 mg, 2.5 mmol) and 5% Pd/$BaSO_4$ (79 mg) were stirred in hexanes (48 mL) under 1 atm of hydrogen. The reduction was monitored by TLC and stopped as soon as no more starting material could be detected. The mixture was filtrated through Celite and concentrated in vacuo, and the residue was chromatographed to yield **3** as a pale yellow oil that crystallized as off-white needles in cold hexanes (425 mg, 52% yield from **6**); mp 82−83 °C (hexanes); TLC R_f 0.34 (petroleum ether−ethyl acetate, 9:1); ^{1}H NMR δ 0.91 (m, 2H), 1.05 (m, 2H), 1.34 (s, 6H), 1.36 (s, 9H), 2.04 (m, 1H), 3.02 (t, 2H, $J = 6.34$ Hz), 3.24 (t, 2H, $J = 6.34$ Hz), 4.30 (s, 2H), 7.64 (d, 1H, $J = 1.95$ Hz), 7.80 (d, 1H, $J = 1.95$ Hz); ^{13}C NMR δ u 209.7, 197.2, 161.7, 137.6, 132.9, 130.1, 84.8, 41.1, 37.0, 34.3, 32.1, 10.8; ^{13}C NMR δ d 126.5, 120.8, 29.2, 27.7, 20.8; IR (film) 2959, 1699, 1674 cm^{-1}; MS (NH_3 − CI, 70 eV) *m*/*z* 231.2 (100), 259.2 (10), 313.2 (11), 329.3 (M + H^{+}, 44); HRMS calcd for $C_{21}H_{28}O_3$ (M^{+}) 328.2038, found 328.2042.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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