J|A|C|S
COMMUNICATIONS

Published on Web 03/01/2005

A Pentenyl Dianion-Based Strategy for Convergent Synthesis of Ene-1,5-diols

Adilah B. Bahadoor, Alec Flyer, and Glenn C. Micalizio*

Sterling Chemistry Laboratory, Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

Received January 4, 2005; E-mail: glenn.micalizio@yale.edu

Efforts directed at the development of efficient synthetic strategies for the synthesis of polyketide-based molecular architecture have led to the discovery and development of many stereoselective carbon−carbon bond-forming processes.[1] Advances made in iterative aldol, allyl-, and allenylmetal-based methods have enabled the syntheses of complex polyketide targets. However, whereas a variety of linear strategies for polypropionate assembly exist, convergent approaches lie primarily in the area of aldol methodology. This limitation dictates the use of fragment coupling processes that result in the formation of a central β-hydroxy ketone.[2] Consequently, more flexible strategies for convergent assembly of polypropionates are needed.[3]

Polypropionate architecture is a common structural motif found in a variety of natural products that possess potent and diverse biological activities. Importantly, members of this class often contain a variety of oxidation and substitution patterns along the polypropionate skeleton including trisubstituted olefins, 1,2-diols, tertiary alcohols, epoxides, and deoxypropionate units. Currently, many of these differentially functionalized polypropionate structural motifs present a barrier that precludes targeting convergent molecular assembly at these sites.

To fill this void we sought to develop a general pentenyl dianion-based strategy for the assembly of highly functionalized ene-1,5-diols of general structure **1** (Figure 1). We envisioned a two-step procedure whereby a synthetic equivalent of the pentenyl dianion **4** could serve to unite two differentially functionalized aldehydes (**2** and **3**) and provide direct access to a functionalized polypropionate. Importantly, the potential for subsequent stereoselective functionalization of the central trisubstituted olefin[4,5] is expected to greatly increase the versatility of this convergent strategy in complex molecule synthesis and thereby complement well-established aldol-based methods.

To accomplish this goal, we set out to develop a two-step process that would allow for: *(1) Diastereoselective propargylation (**5** → **6**), (2) carbon−carbon bond formation in the presence of a free hydroxyl (**6** → **8**), (3) regioselective reductive coupling (**6** → **8**), and (4) diastereoselective reductive coupling (**6** → **8**).* In this fashion, the ene-1,5-diol **8** would be available in two steps (from aldehydes **5** and **7**) whereby two carbon−carbon bonds, three new stereogenic centers, and one stereodefined trisubstituted olefin are established—all without the need for intermediate protecting-group manipulations. This communication describes our preliminary results aimed at realizing this convergent strategy for polypropionate assembly.

First, to address versatility in this convergent two-step process, we required general and selective access to all stereoisomers of the homopropargylic alcohol component (**6**; Figure 1). As such, we focused on application of chiral allenylmetal reagents in double asymmetric[6] propargylation reactions with chiral aldehydes.[7] Although diastereoselective propargylation reactions of chiral aldehydes with chiral allenylmetal reagents have been well studied, these processes using a 2,3-pentadiene-based organometallic (**16**) have

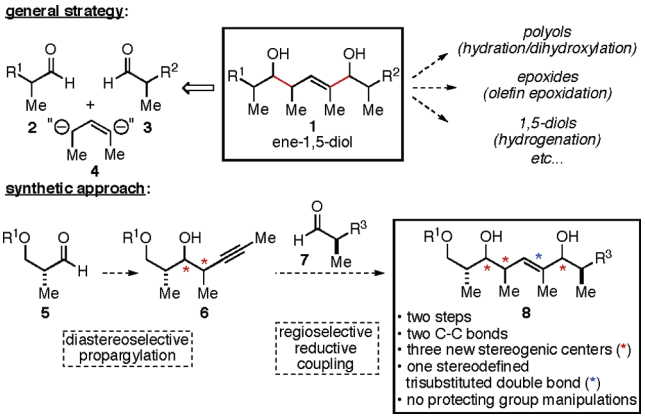


Figure 1. Two-step sequence to access a pentenyl dianion equivalent.

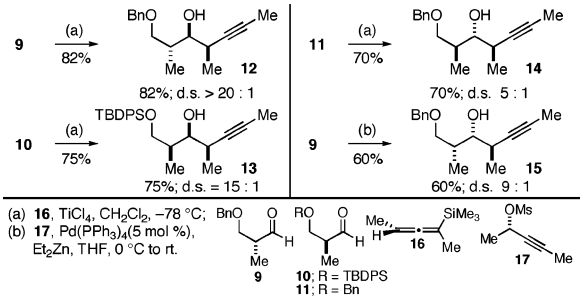


Figure 2. Stereochemical flexibility of diastereoselective propargylation.

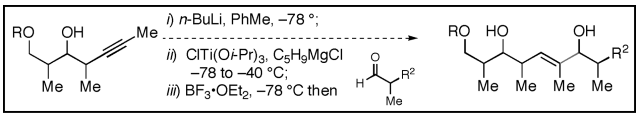
received relatively little attention.[8] As described in Figure 2, these reagents provide general and stereoselective access to all stereoisomers of the homopropargylic alcohol component **12**−**15** (ds > 20:1 to 5:1).[9]

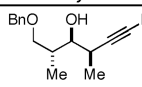
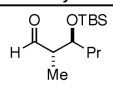
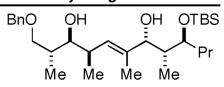
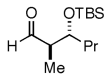
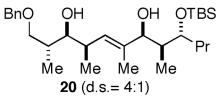
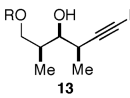
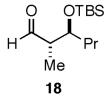
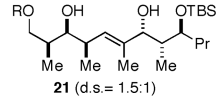
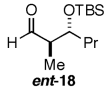
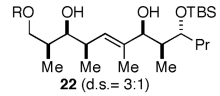
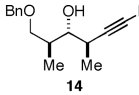
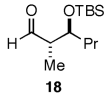
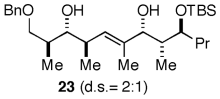
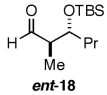
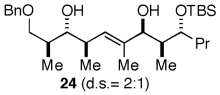
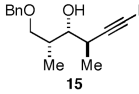
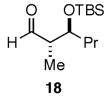
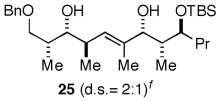
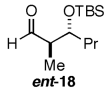
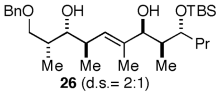
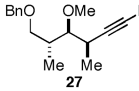
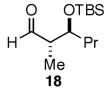
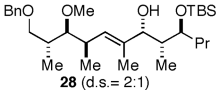
After a stereochemically flexible route to the required homopropargylic alcohols (**12**−**15**) was secured, attention was directed toward defining a reductive coupling process that would enable the general conversion **6** → **8** described in Figure 1.[10] For this purpose we selected low-valent titanium alkoxide-based methods, as we suspected that these reagents would allow for reductive coupling with a carbonyl electrophile in the presence of an alkoxide.[11] As described in Table 1 (entry 1), deprotonation of the *syn*−*anti* homopropargylic alcohol **12**, followed by exposure to the combination of chlorotitanium triisopropoxide and cyclopentylmagnesium chloride, then addition $BF_3{\cdot}OEt_2$ and aldehyde **18**, provided the ene-1,5-diol **19** in 66% yield (ds 1.5:1) with high regioslectivity (rs 19:1).

Next, the generality of this new highly regioselective reductive coupling process was explored as a strategy for the synthesis of stereochemically diverse polypropionates. As such, the four stereoisomeric homopropargylic alcohols **12**−**15** were coupled with each enantiomer of a 2,3-*anti*-aldehyde (**18** and ***ent*-18**). Regioselection was high in most cases (19:1 to 7:1) and provided the ene-1,5-diol products **19**−**26** as mixtures of diastereomers uniformly favoring

10.1021/ja050039+ CCC: $30.25

Table 1. Application to the Synthesis of Complex Polypropionates



entry	alkyne	aldehyde	yield[a]	r.s.[b]	major regioisomer[c]
1	 **12**	 **18**	66	19:1	 **19** (d.s.= 1.5:1)
2	**12**	 ***ent*-18**	65	13:1	 **20** (d.s.= 4:1)
3	 **13**	 **18**	55	16:1	 **21** (d.s.= 1.5:1)
4	**13**	 ***ent*-18**	50	7:1[f]	 **22** (d.s.= 3:1)
5	 **14**	 **18**	65	19:1	 **23** (d.s.= 2:1)
6[d]	**14**	 ***ent*-18**	62	8:1	 **24** (d.s.= 2:1)
7	 **15**	 **18**	60	5:1	 **25** (d.s.= 2:1)[f]
8[d]	**15**	 ***ent*-18**	42	3:1	 **26** (d.s.= 2:1)
9[e]	 **27**	 **18**	71	13:1	 **28** (d.s.= 2:1)

[a] Yield reported for major regioisomer. [b] Regioselectivity determined by ^{1}H NMR of the crude reaction mixture. [c] Major diastereomer is depicted. [d] Addition of RCHO at −100 °C. [e] Deprotonation step not performed. [f] Selectivity determined after isolation.

the Felkin products (generally ≥2:1).[12] Interestingly, *levels of regioselectivity were observed to be a function of both the relative stereochemistry of the homopropargylic alcohol and the absolute stereochemistry of the aldehyde*.[13] Whereas high regioselectivity was observed in most cases, highest levels of regioselection for coupling of each homopropargylic alcohol were observed in the formation of coupled products bearing a 1,5-*anti* stereochemical relationship between the allylic and homoallylic methyl substituents (entries 1, 3, 5, and 7). Finally, to probe the significance of the homopropropargylic alkoxide in these regioselective coupling reactions we examined the union of the methyl ether **27** with aldehyde **18** (entry 9). Similarly, high regioselectivity was observed in this case, thereby indicating that the presence of a neighboring alkoxide is not required for high levels of regioselection.[14,15]

Overall, we have defined a two-step procedure that enables convergent assembly of 1,5-diols and extends the utility of allenylmetal reagents to formal pentenyl dianion equivalents through a process that establishes three new stereogenic centers and one stereodefined trisubstituted olefin. Our preliminary studies have defined: (1) the stereochemical flexibility of propargylation (***5*** → ***6***), (2) a reductive coupling process with chiral aldehydes that is tolerant of free hydroxyls—a factor which is projected to lead to increased efficiency in polypropionate synthesis, (3) highly regioselective reductive coupling reactions of internal alkynes that allow for convergent assembly of polypropionates, and (4) defined the levels of diastereoselection in these coupling processes based on substrate control. Our successes in these areas have provided impetus for future studies aimed at enhancing levels of diastereoselection in this highly regioselective reductive coupling process.

Finally, we have observed that the stereochemical relationship between the aldehyde and the homopropargylic alcohol influences levels of *regioselection* in these complex reductive coupling reactions. This unusual manifestation of double asymmetric control[6] is a facet of these processes that will be explored in more detail in future studies. Overall, this formal pentenyl dianion-based strategy is anticipated to expand flexibility in the design of convergent approaches toward the synthesis of complex polyketide-derived targets. Progress along these lines will be reported in due course.

Acknowledgment. We gratefully acknowledge financial support of this work by Yale University and Eli Lilly & Co. We also thank Novartis for a graduate fellowship to A.B.B.

Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Otera, J., Ed. *Modern Carbonyl Chemistry*; Wiley-VCH: Weinheim, 2000.
(2) Selected examples of convergent synthesis of polypropionates: (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073. (b) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447. (c) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082; for reviews see ref 1.
(3) For a convergent approach to ene-1,5-diols centered about a disubstituted olefin, see: Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644 and references therein.
(4) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(5) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(6) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(7) (a) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870. (b) Marshall, J. A.; Maxson, K. J. *J. Org. Chem.* **2000**, *65*, 630. See also: (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.
(8) Buckle, M. J. C.; Fleming, I. *Tetrahedron Lett.* **1993**, *34*, 2383.
(9) See: Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812.
(10) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. See also: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.
(11) (a) Epstein, O. L.; Kulinkovich, O. G. *Tetrahedron Lett.* **1998**, *39*, 1823. (b) Urabe, H.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7329. For reviews see. (c) Kulinkovich, O. G.; Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (d) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (e) Marek, I., Ed. *Titanium and Zirconium in Organic Synthesis*; Wiley-VCH: Weinheim, 2002.
(12) No products were observed that indicated epimerization of the aldehyde.
(13) For an interesting discussion of regioselectivity in allylic alkylation reactions based on diastereomeric π-allyl complexes, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(14) For examples of directed regioselective reductive coupling reactions with nickel complexes, see: (a) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (b) Miller, K. M.; Lauanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. (c) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342.
(15) Reductive coupling reactions of the homopropargylic alcohol **12** with aldehydes lacking α- or β-branching were also regioselective (5:1 to 3:1). See Supporting Information.

JA050039+