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Highly anti-selective conjugate addition of arylcuprates to a γ-alkoxy-α,β-enoate. A new method to address stereochemical challenges presented by Amaryllidaceae alkaloids

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Abstract—Various substituted arylcuprates undergo stereocontrolled additions to a D-mannitol-derived γ-alkoxy-α,β-enoate with exclusive anti-selectivity. The method is well suited for the preparation of a broad range of biologically active Amaryllidaceae alkaloids and their aromatic analogues. A model accounting for the stereochemical outcome of this process is presented.

Isoquinoline alkaloids, isolated from plants of the Amaryllidaceae family, have attracted broad interest from synthetic chemists, biologists, and pharmacologists.[1] Many of these natural products have been found to display various medicinally useful physiological effects including anticancer, antiviral, immunostimulatory, acetylcholinesterase inhibitory, and antimalarial activities. On the basis of the carbon framework, Amaryllidaceae alkaloids are classified into several structural types, examples being the narciclasine, lycorine, and lycorenine families (Fig. 1).

According to a recent comprehensive review, over 100 alkaloids that fall into one of these three groups have been isolated.[2] Despite potent biological activities associated with some of these Amaryllidaceae constituents,

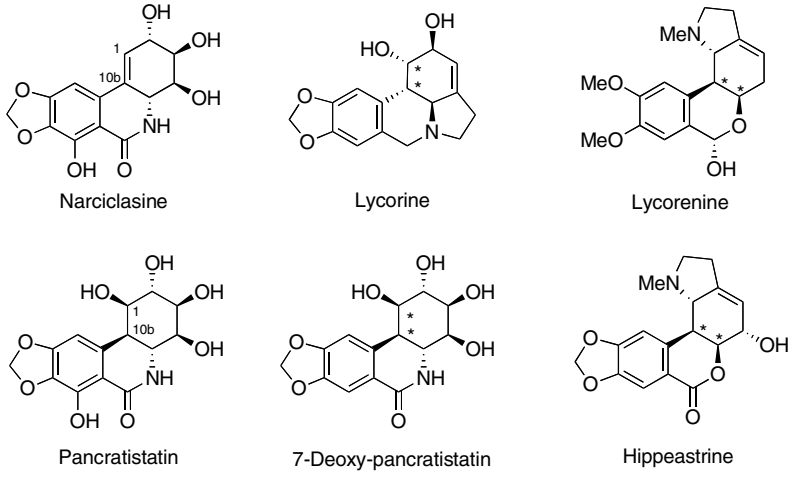

Figure 1.

Keywords: Acyclic stereoselection; Arylcuprate; Amaryllidaceae alkaloids.
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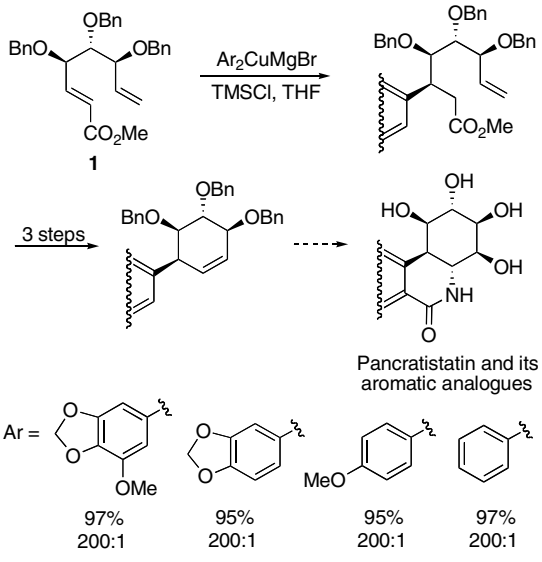
their medicinal evaluation is hampered due to low natural abundance, hence insufficient quantities available from isolation. For example, pancratistatin (narciclasine type) is a potent anticancer, antiviral, and antiparasitic agent that has been in various stages of preclinical development for over 18 years. This lengthy time period is in great part due to availability issues.[3] Cytotoxic alkaloids hippeastrine[4] (lycorenine type) and 7-deoxypancratistatin[5] (narciclasine type) serve as additional examples of this problem. It should be noted that 7-deoxypancratistatin has been shown to exhibit promising therapeutic indexes in antiviral assays and represents a rare example of chemotherapeutic efficacy in a Japanese Encephalitis virus infected mouse model.[6]

These issues have led to a worldwide effort aimed at developing synthetic pathways to these natural products for systematic study of their biology and generation of analogues with medicinal potential. The complexity of these structures stems in part from dense stereochemistry of the cyclitol moiety. Thus, installation of the aromatic ring with the required stereochemistry in pancratistatin (position C10b) has significantly undermined the efficiencies of its published syntheses.[7] Consequently, pancratistatin's practical chemical preparation, which will provide the required quantity of material for clinical trials, still captivates the minds of the synthetic community.[8] In contrast, much shorter synthetic approaches have been developed to narciclasine, which has no stereocenter at position C10b.[9]

Our recently disclosed synthetic strategy for a practical synthesis of pancratistatin involves an arylcuprate conjugate addition process to γ,δ,ε-trialkoxyenoate **1** (Scheme 1) as an efficient way to install the C10b stereocenter.[10] We found that this reaction affords exclusive anti-selectivity, independent of the substitution pattern on the aromatic ring. While the anti-stereochemical outcome of this process makes it potentially applicable to the synthesis of lycorine and lycorenine alkaloid types,[11] we were uncertain about the contribution of δ and ε-benzyloxy groups in enoate **1** toward this high selectivity. This is an important issue since successful application of this arylcuprate chemistry in various settings requires that efficient stereocontrol be exerted by a single γ-alkoxy group.



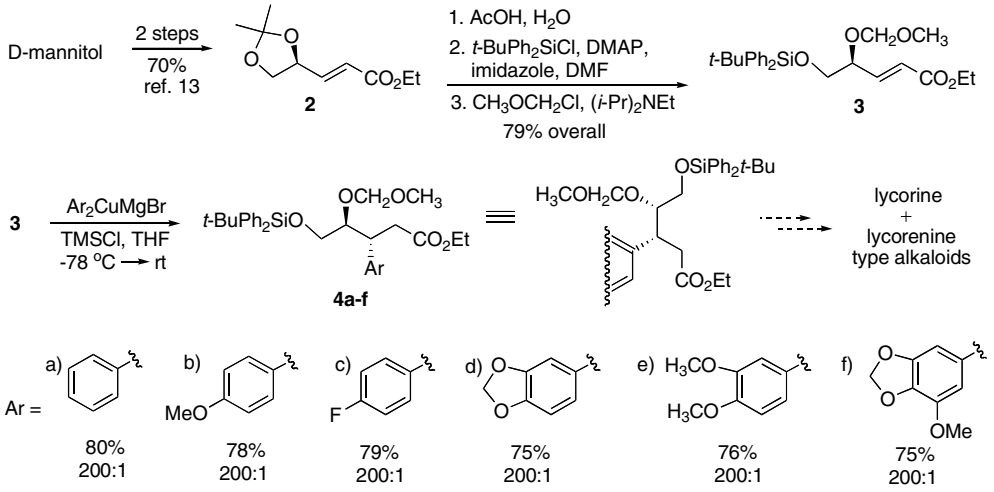
Scheme 1.

Examination of the literature reports of organocopper addition processes with γ-alkoxy-α,β-enoates reveals that although the anti-stereochemical outcome is cwell-precedented, the selectivities range from moderate to high and are seldom exclusive.[12] While various γ-oxygen protecting groups have been found to favor the formation of anti-products, Hanessian and his coworkers systematically studied Me_2CuLi addition to a glyceraldehyde-derived enoate and found that selectivities were highest with methoxymethyl (10:1) and benzyloxymethyl (14:1) groups.[12d] Although Ph_2CuLi reagent was only moderately (4.5:1) anti-selective with a γ-MOMO-α,β-enoate,[12d] the same research group reported later that the reaction of $Ph_2CuMgBr$ with a γ-BOMO-α,β-enoate displayed very high anti-selectivity.[12k] These, to our knowledge, represent the only examples of utilization of arylcuprates in this methodology.

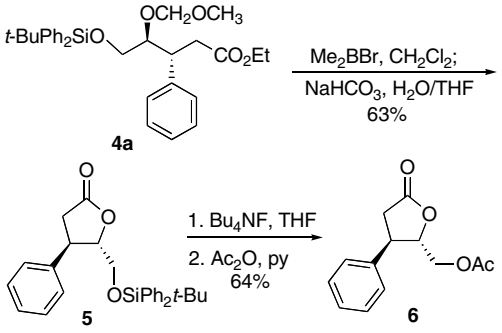
The above-mentioned reports prompted us to prepare enoate **3** utilizing literature procedures reported for a related compound[12d,13] and investigate its reactions with various substituted arylcopper reagents, including those derived from alkoxy aromatics (Scheme 2). We were pleased to find that under the reaction conditions previously developed for enoate **1**, these additions proceed with exclusive anti-diastereoselectivities[14] with all of the arylcuprates studied.[15,16]

The anti-stereochemistry was confirmed by converting the phenyl addition product **4a** to known lactone **6**, whose ^1H and ^{13}C NMR had been previously reported (Scheme 3).[17]

A number of transition state models, which may account for anti-selective addition of alkyl, vinyl, and allyl cuprates to γ-alkoxy-α,β-enoates, have been discussed by various investigators.[12b,d,e] Clearly, because of the complex and diverse nature of organocopper reagents, no single mechanistic model generally explains or predicts the outcome of these reactions. In addition, the results of recent mechanistic investigations strongly support the involvement of large cluster frameworks in these conjugate additions.[18] Thus, the reason for the strong anti-stereochemical preference may be totally different for arylcuprates. The rather unusual (for acyclic systems) high degree of stereocontrol observed here leads us to favor a 'modified Felkin-Anh'[19] interpretation (Fig. 2), in which allylic 1,3-strain[20] greatly destabilizes transition state **B** that leads to syn-products. This destabilization is augmented by the 'acute' angle of attack in a copper-enoate π-complex, whose formation is evidenced by recent experimental and theoretical work (Fig. 2).[18,21] To our knowledge, there has been no discussion of factors determining stereochemical outcome of such reactions after the new mechanistic understanding



Scheme 2.



Scheme 3.

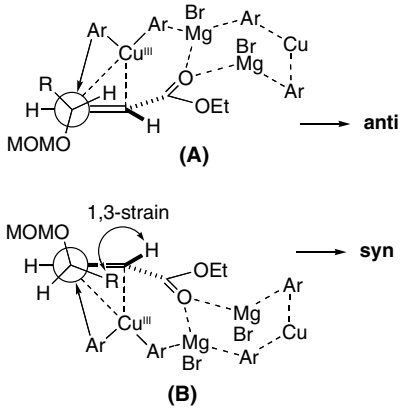


Figure 2.

of organocopper conjugate addition process, including the intermediacy of Cu^{III} species, has emerged.

We believe that the chemistry described in this letter will find general utility in procedures for the installation of aromatic subunits with required stereochemistry in pathways to a large number of medicinally promising Amaryllidaceae alkaloids and other stereochemically complex substances. Two particular aspects of this method are noteworthy. Firstly, the observed exclusive stereocontrol is an important factor in evaluating the potential scalability of any synthetic method, since normally difficult chromatographic separation of acyclic stereoisomers is not required. Secondly, the lack of dependence of this stereochemical outcome on the substitution pattern on the aromatic ring makes this process applicable to the generation of aromatic analogues of these natural products, an area which has been little explored.[22]

Further efforts are underway in this area to apply this chemistry to the synthesis of Amaryllidaceae constituents and to refine the presented stereochemical model.

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Supplementary data

The supplementary data, which include the copies of ^{1}H and ^{13}C NMR spectra of compounds **3** and **4a**–**f**, are available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.006.

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14. We were unable to detect the presence of syn isomers in reaction product mixtures.
15. General procedure for the arylcuprate additions: ca. 1 mL of a required aryl bromide (7.03 mmol) was added to crushed Mg turnings (7.03 mmol, 0.17 g) in THF (10 mL) under nitrogen atmosphere. Once the reaction started, the solution warmed up and slightly darkened. The rest of the aryl bromide was added dropwise to allow a gentle reaction. The reaction mixture was allowed to cool to room temperature and was cannulated to a slurry of CuI (3.52 mmol, 0.67 g) in THF (10 mL) at −78 °C. The mixture was stirred at −78 °C for 40 min (in the synthesis of **4e** the mixture was stirred at 0 °C for 2 h, as no transmetallation occurred at −78 °C). Me_3SiCl (7.03 mmol, 0.76 g) and enoate **3** (0.703 mmol, 0.311 g in 10 mL of THF) were added sequentially at −78 °C. The yellow-brown suspension was stirred overnight while slowly warming up to room temperature. The reaction mixture was quenched with a mixture of concd. NH_4OH and satd NH_4Cl (1:9, 30 mL) and extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was absorbed on silica gel and purified by column chromatography (5–10% EtOAc/hexanes) to yield **4a**–**f** as an oil.
16. Characterization data: **3**: R_f 0.64 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ +12.3 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38–7.69 (m, 10H), 6.85 (dd, 1H, *J* = 5.5, 15.7 Hz), 6.06 (dd, 1H, *J* = 1.4, 15.7 Hz), 4.72 (d, 1H, *J* = 6.6 Hz), 4.65 (d, 1H, *J* = 6.6 Hz), 4.32 (m, 1H), 4.16 (q, 2H, *J* = 7.1 Hz), 3.71 (dd, 1H, *J* = 6.6, 10.5 Hz), 3.63 (dd, 1H, *J* = 5.2, 10.7 Hz), 3.35 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.2, 145.2, 135.7, 133.2, 129.9, 127.8, 122.9, 95.3, 76.0, 66.1, 60.5, 55.7, 26.8, 19.3, 14.3; HRMS *m/z* (ESI) calcd for $C_{25}H_{34}O_5SiNa$ ($M+Na^+$) 465.2067, found 465.2063. **4a**: R_f 0.58 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ −43.9 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.19–7.60 (m, 15H), 4.68 (d, 1H, *J* = 6.9 Hz), 4.51 (d, 1H, *J* = 6.9 Hz), 3.97 (q, 2H, *J* = 7.2 Hz), 3.75 (m, 1H), 3.46 (m, 3H), 3.27 (s, 3H), 2.97 (dd, 1H, *J* = 5.2, 15.6 Hz), 2.64 (dd, 1H, *J* = 10.2, 15.6 Hz), 1.08 (t, 3H, *J* = 7.2 Hz), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 141.3, 135.5, 133.2, 129.8, 128.5, 127.8, 126.9, 96.4, 81.0, 63.9, 60.0, 56.0, 43.1, 37.2, 26.8, 19.2, 14.0; HRMS *m/z* (ESI) calcd for $C_{31}H_{40}O_5SiNa$ ($M+Na^+$) 543.2537, found 543.2530. **4b**: R_f 0.45 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ −45.7 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.76–7.60 (m, 14H), 4.52 (d, 1H, *J* = 6.9 Hz), 4.69 (d, 1H, *J* = 6.9 Hz), 3.98 (q, 2H, *J* = 7.0 Hz), 3.77 (s, 3H), 3.75 (m, 1H), 3.42 (m, 3H), 3.29 (s, 3H), 2.96 (dd, 1H, *J* = 5.2, 15.4), 2.59 (dd, 1H, *J* = 10.5, 15.4 Hz), 1.07 (t, 3H, *J* = 7.0 Hz), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 158.4, 135.7, 135.6, 133.4, 133.2, 129.7, 129.3, 127.7, 116.1, 114.8, 113.8, 96.4, 81.1, 63.7, 60.2, 56.1, 55.3, 42.6, 37.4, 26.9, 19.3, 14.2; HRMS *m/z* (ESI) calcd for $C_{32}H_{42}O_6SiNa$ ($M+Na^+$) 573.2642, found 573.2630. **4c**: R_f 0.48 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ −37.8 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.63–6.92 (m, 14H), 4.67 (d, 1H, *J* = 6.9 Hz), 4.50 (d, 1H, *J* = 6.9 Hz), 3.99 (q, 2H, *J* = 7.1 Hz), 3.71 (m, 1H), 3.52 (m, 3H), 3.27 (s, 3H), 2.97 (dd, 1H, *J* = 4.9, 15.7 Hz), 2.60 (dd, 1H, *J* = 10.5, 15.7 Hz), 1.07 (t, 3H, *J* = 7.1 Hz), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.4, 136.9, 135.7, 135.5, 133.3, 133.1, 129.9, 129.8, 127.7, 115.4, 115.1, 96.4, 80.8, 63.6, 60.3, 56.1, 42.6, 37.1, 31.0, 26.9, 19.2, 14.2; HRMS *m/z* (ESI) calcd for $C_{31}H_{39}FO_5SiNa$ ($M+Na^+$) 561.2443, found 561.2422. **4d**: R_f 0.46 (20% EtOAc/hexanes); $[\alpha]_D^{21}$ −35.59 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.59–7.30 (m, 10H), 6.66 (m, 3H), 5.91 (s, 2H), 4.70 (d, 1H, *J* = 6.9 Hz), 4.53 (d, 1H, *J* = 6.9 Hz), 4.0 (q, 2H, *J* = 7.2 Hz), 3.69 (m, 1H), 3.51 (m, 3H), 2.94 (dd, 1H, *J* = 4.95, 15.4 Hz), 2.56 (dd, 1H, *J* = 10.2, 15.4 Hz), 1.12 (t, 3H, *J* = 7.2 Hz), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 147.8, 146.3, 135.6, 133.7, 129.7, 127.7, 121.8, 108.3, 108.0, 100.9, 96.5, 81.7, 64.0, 60.3, 56.0, 35.8, 34.7, 31.7, 26.9, 25.3, 22.7, 14.2; HRMS *m/z* (ESI) calcd for $C_{32}H_{40}O_7SiNa$ ($M+Na^+$) 587.2435, found 587.2421. **4e**: R_f 0.38 (20% EtOAc/

hexanes); $[\alpha]_D^{21}$ −26.8 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.63–7.28 (m, 10H), 6.73 (m, 3H), 4.69 (d, 1H, J = 6.9 Hz), 4.52 (d, 1H, J = 6.9 Hz), 3.99 (q, 2H, J = 7.7 Hz), 3.85 (s, 3H), 3.78 (s, 3H), 3.73 (m, 1H), 3.52 (m, 3H), 3.30 (s, 3H), 2.97 (dd, 1H, J = 4.9, 15.4 Hz), 2.61 (dd, 1H, J = 10.5, 15.4 Hz), 1.11 (t, 3H, J = 7.7 Hz), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 148.7, 147.7, 135.6, 133.7, 133.4, 133.1, 129.8, 127.7, 120.3, 111.5, 111.0, 96.4, 81.0, 63.7, 60.2, 56.1, 55.9, 43.0, 37.6, 26.9, 19.3, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{33}H_{44}O_7SiNa$ ($M+Na^+$) 603.2748, found 603.2764. **4f**: R_f 0.56 (40% EtOAc/hexanes); $[\alpha]_D^{21}$ −27.2 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.61–7.30 (m, 10H), 6.38 (m, 2H), 5.92 (s, 2H), 4.69 (d, 1H, J = 6.7 Hz), 4.52 (d, 1H, J = 6.7 Hz), 4.02 (q, 2H, J = 6.9 Hz), 3.79 (s, 3H), 3.68 (m, 1H), 3.50 (m, 3H), 3.29 (s, 3H), 2.94 (dd, 1H, J = 4.9, 15.4 Hz), 2.56 (dd, 1H, J = 10.2, 15.4 Hz), 1.13 (t, 3H, J = 6.9 Hz), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 148.7, 143.3, 135.8, 135.7, 135.5, 133.9, 133.3, 133.1, 129.7, 127.7, 107.7, 102.1, 101.4, 96.4, 80.9, 63.7, 60.3, 56.4, 56.1, 43.4, 37.4, 26.8, 19.2, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{33}H_{42}O_8SiNa$ ($M+Na^+$) 617.2541, found 617.2551.

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