

Conjugate Addition of 2- and 4-Pyridylcuprates: An Expedient Asymmetric Synthesis of Natural (–)-Evoninic Acid

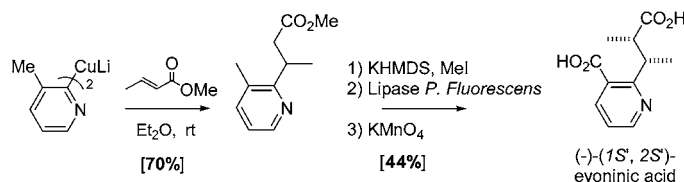
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ABSTRACT



The scope and limitations of the conjugate addition of 2- and the first 4-pyridyl Gilman homocuprates to various α,β -unsaturated Michael acceptors are delineated. The conjugate addition of the cuprate of 2-bromo-3-methylpyridine to (*E*)-methyl crotonate then diastereoselective enolate alkylation and lipase-mediated enantioselective ester hydrolysis have enabled an efficient four-step first asymmetric synthesis of the Celastraceae sesquiterpenoid esterifying ligand (–)-(1′*S*,2′*S*)-evoninic acid.

Crude extracts of the Celastraceae have been used in traditional Chinese medicine for hundreds of years, notably for the treatment of cancers.¹ Among the secondary metabolites isolated from these plant extracts, a large family polyesterified sesquiterpenoids based on the octahydroxy- β -dihydroagarofuran euonyminol (**1**) have attracted recent interest due to their anti-HIV, antitumor, and immunosuppressive activities [e.g., hyponine B (**2**),² emarginatine F (**3**),³ and ebenifoline E-II (**4**)].^{4,5} These natural products, and other evoninate-type Celastraceae sesquiterpenoids, contain a macrodilactone bridge between C3 and C13 comprising

the pyridyl diacid residue, (–)-(1′*S*,2′*S*)-evoninic acid (**6s**, Figure 1).⁶

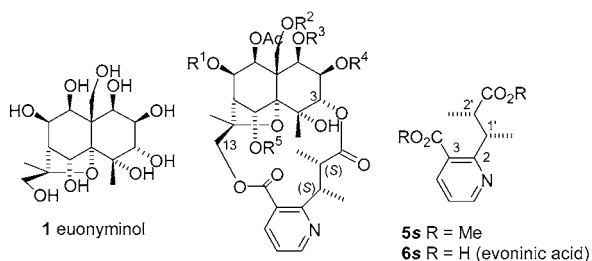


Figure 1. Structures of euonyminol, some derived bioactive Celastraceae sesquiterpenoids, and evoninic acid.

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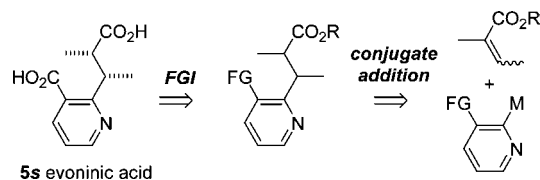
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As part of a program aimed at the total synthesis of bioactive sesquiterpenoids of the Celastraceae,⁷ we required an efficient synthesis of natural (–)-(1′S,2′S)-evoninic acid (**6s**). Since the only literature synthesis provides (±)-evoninic acid (**6s**) in ~1.8% overall yield (six steps) from noncommercially available 3-amino-pent-2-enoic acid ethyl ester and requires preparative GC separation of dimethylevoninate from its *anti* diastereoisomer (dr = 39:61, **5s/5a**),⁸ we decided to explore a *de novo* route via conjugate addition of a 2-pyridyl metal derivative to an enoate (Scheme 1).

Scheme 1. Envisaged Approach to the Synthesis of Evoninic Acid **6s**: Retrosynthetic Analysis



We report herein the results of these studies in which the scope of not only 2- but also the first 4-pyridyl cuprate conjugate additions to enones/enoates has been delineated. An expedient asymmetric synthesis of (–)-(1′S,2′S)-evoninic acid using this methodology is then described.

Conjugate addition of aryls to unsaturated carbonyl-containing compounds is generally achieved using Rh-catalyzed aryl boronates/stannanes (and related species),⁹ Cu-catalyzed aryl zinc/Grignard reagents,¹⁰ or stoichiometric aryl lithium cuprates.¹¹ Given the prevalence of pyridyl rings in pharmacologically interesting structures, we were surprised to find no reports of either Rh- or Cu-catalyzed pyridine additions and very few reports of the use of pyridyl cuprates (none of which involved 4-pyridyl cuprates).^{11,12} Of note, however, were three reports by Nilsson in the 1980s describing the conjugate addition of Gilman homo- and heterocuprates of 2-bromopyridine to (*E*)-1-phenyl-1-buten-3-one, (*E*)-5-phenyl-2,2-dimethyl-4-penten-3-one, and (*E*)-ethyl cinnamate in good yields.^{13–15} We therefore decided to explore the scope of 2- and also 4-pyridyl cuprate additions

to enones/enoates. In particular, tolerance of substitution at C3 of the pyridine ring and at all positions on the alkene moiety of the Michael acceptor was of interest. Addition reactions of 2-pyridyl cuprates, as pioneered by Nilsson, were investigated first (Table 1).

Table 1. Conjugate Addition of 2-Pyridyl Gilman Homocuprates to α,β -Unsaturated Substrates

#	R ¹	R ²	R ³	R ⁴	yield/%
1	H (7a)	Ph	H	CO ₂ Et (8a)	80 (9a) ^d
2	H (7a)	Me	H	CO ₂ Me (8b)	79 (9b)
3	H (7a)	Me	Me	CO ₂ Me (8c)	69 (9c) ^b
4	Me (7b)	Me	H	CO ₂ Me (8b)	70 (9d)
5	Me (7b)	Me	Me	CO ₂ Me (8c)	10 (9e) ^c
6	vinyl (7c)	Me	H	CO ₂ Me (8b)	-
7	CH(OCH ₂ CH ₂ O) (7d)	Me	H	CO ₂ Me (8b)	-
8	CH ₂ OMe (7e)	Me	H	CO ₂ Me (8b)	-
9	H (7a)	Me	H	COMe (8d)	80 (9f)
10	Me (7b)	Me	H	COMe (8d)	85 (9g)
11	Me (7b)	Me	H	CN (8e)	81 (9h)

^a Cf. Nilsson, 82% (ref 13). ^bdr = 20:80, *syn/anti* (**9cs/9ca**). ^cdr = 23:77, *syn/anti* (**9es/9ea**). The (*Z*)-isomer, methyl angelate, gave dr = 63:37 (**9es/9ea**) in 14% yield.

Using the 3-unsubstituted 2-pyridyl cuprate derived from 2-bromopyridine (**7a**), conjugate addition proceeded smoothly with (*E*)-ethyl cinnamate (**8a** → **9a**, 80% yield, Table 1, entry 1), (*E*)-methyl crotonate (**8b** → **9b**, 79% yield, Table 1, entry 2), methyl tiglate (**8c** → **9c**, 69% yield, Table 1, entry 3), and (*E*)-3-penten-2-one (**8d** → **9f**, 80% yield, Table 1, entry 9). By contrast, of the four 2-pyridyl cuprates containing substituents at C3 that were investigated (i.e., derived from 2-bromopyridines **7b–e**), only the one with a 3-methyl group (i.e., derived from 2-bromo-3-methylpyridine, **7b**) participated in conjugate addition reactions successfully (Table 1, entries 4, 5, 10, and 11). Thus, reactions of this cuprate with (*E*)-methyl crotonate (**8b**, Table 1, entry 4), methyl tiglate (**8c**, Table 1, entry 5), methyl angelate (Table 1, entry 5, footnote c), (*E*)-3-penten-2-one (**8e**, Table 1, entry 10), and (*E*)-crotononitrile (**8e**, Table 1, entry 10) gave yields of 70%, 10%, 14%, 85%, and 81%, respectively. The low yields obtained when using methyl tiglate and angelate probably reflect the high steric demand of these substrates. The failure of the reactions using 3-vinyl- (**7c**), 3-CH(OCH₂CH₂O)- (**7d**), and 3-methoxymethyl- (**7e**) substituted 2-bromopyridine-derived cuprates, despite extensive attempted optimization of the conditions of the reactions, probably reflects either coordinative stabilization of these cuprates by the appendages or, again, steric hindrance.

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4-Pyridyl cuprates required slightly more dilute conditions, and in the case of the unsubstituted 4-pyridyl cuprate reagent, freshly prepared 4-iodopyridine (**7f**) proved a superior precursor to 4-bromopyridine. We were delighted to find that these reagents added smoothly to various Michael acceptors (Table 2).

Table 2. Conjugate Addition of 4-Pyridyl Gilman Homocuprates to α,β -Unsaturated Substrates

#	R ¹	X	R ²	R ³	R ⁴	yield/%
1	H (7f)	I	Me	H	CO ₂ Me (8b)	78 (9i)
2	H (7f)	I	Me	Me	COMe (8d)	86 (9j)
3	H (7f)	I	Me	H	CN (8e)	90 (9k)
4	Me (7g)	Br	Me	H	CO ₂ Me (8b)	65 (9l)
5	Me (7g)	Br	Me	H	COMe (8d)	82 (9m)
6	Me (7g)	Br	Me	H	CN (8e)	69 (9n)
7	Br ^a (7h)	H	Me	H	COMe (8d)	79 (9o)

^a 3-Bromopyridine.

Thus, the 4-iodopyridine-derived (**7f**) cuprate added smoothly to (*E*)-methyl crotonate (**8b** → **9i**, 78% yield, Table 2, entry 1), (*E*)-3-penten-2-one (**8d** → **9j**, 86% yield, Table 2, entry 2), and (*E*)-crotononitrile (**8e** → **9k**, 90% yield, Table 2, entry 3). The 4-bromo-3-methylpyridine-derived cuprate added with only slightly diminished facility to these substrates (65%, 82%, and 69% respectively, Table 2, entries 4–6). The addition of the cuprate derived from 3-bromopyridine (**7h**) to (*E*)-3-penten-2-one (**8d**) was also successful (86% yield, Table 2, entry 7), although we did not explore any substituted analogues or other substrates in this series.

With the conjugate addition method established, we returned to the synthesis of evoninic acid. Given the intolerance of the conjugate addition process to groups other than methyl at C3 of 2-pyridyl cuprates and the poor yields obtained with methyl tiglate and angelate, it was clear that our synthesis of evoninic acid would need to be based on the conjugate addition of the pyridyl cuprate derived from 2-bromo-3-methylpyridine (**7b**) to (*E*)-methyl crotonate (Table 1, entry 4). Completion of the synthesis from pyridyl ester **9d** required diastereoselective methylation at C2', ester hydrolysis, and selective benzylic oxidation of the pyridyl methyl group to the corresponding carboxylic acid.

A number of conditions were assayed for the methylation of ester **9d** at C2' (Table 3).

Methylation using LDA/MeI in THF from –40 °C to room temperature¹⁶ afforded esters **9es** and **9ea** as an inseparable mixture of diastereoisomers [dr = 40:60, *syn/anti* (**9es/9ea**)]

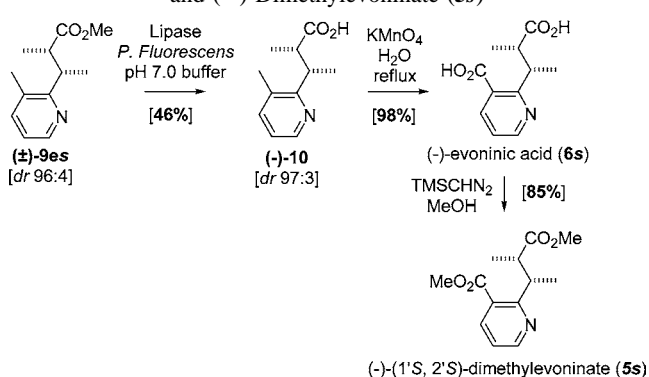
Table 3. Methylation of Ester **9d**

#	conditions	<i>syn:anti</i>	yield/%
1	LDA, MeI, THF, –40 → 25 °C, 1 h	40:60	98
2	LDA, MeI, THF, –78 °C, 24 h	33:67	98
3	LDA, MeI, Tol, –40 → 25 °C, 1 h	57:43	97
4	KHMDS, MeI, Tol, –40 → 25 °C, 1 h	87:13	96
5	KHMDS, MeI, Tol, –78 °C, 24 h	96:4	98

(Table 3, entry 1). Lowering the temperature (Table 3, entry 2) and changing the solvent to toluene (Table 3, entry 3) had no appreciable effect on the selectivity. However, using KHMDS in toluene rather than LDA strongly favored the formation of the desired *syn* diastereoisomer particularly at low temperature [dr = 87:13 at room temperature and 96:4 at –78 °C] (Table 3, entries 4 and 5).¹⁷

Following screening of a panel of hydrolytic enzymes,¹⁸ we found that lipase from *Pseudomonas fluorescens* was able to effect a highly efficient enantioselective hydrolysis of ester (\pm)-**9es** in a pH 7 phosphate buffer at 37 °C. This procedure afforded acid (–)-**10s** (46% yield, dr 97:3, >95% ee)¹⁹ by simple extraction from the crude reaction mixture after 48 h. Oxidation of acid (–)-**10s** using KMnO₄ gave (–)-evoninic acid **6s** in 98% yield [four steps, 31% overall yield from 2-bromo-3-methylpyridine (**7b**)]. The absolute configuration was assigned by conversion to (–)-(1'*S*,2'*S*)-dimethylevoninate (**5s**, [α]_D²⁰ –41.1 (c 0.14 in CHCl₃); cf. lit.⁶ [α]_D²⁰ –42) using TMSCHN₂ (85% yield, Scheme 2).

Scheme 2. Conversion of Ester **9d** into (–)-Evoninic Acid (**6s**) and (–)-Dimethylevoninate (**5s**)



The absolute configuration of this derivative has been established by chemical correlation to (+)-2,3-dimethylsuccinic anhydride⁶ and also by anomalous dispersion single-crystal X-ray structure determination of bromoacetylneononine.²⁰

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In summary, the scope of the conjugate addition of 2-pyridyl Gilman homocuprates to enones/enoates, first developed by Nilsson, has been further explored with respect to tolerance of substitution at C3 of the pyridine ring and with respect to substituents on the alkene moiety of the Michael acceptor. Additionally, the first conjugate addition reactions of 4-pyridyl Gilman homocuprates to enones/enoates have been described. The utility of the methodology has been underscored by employing the conjugate addition of the cuprate derived from 2-bromo-3-methylpyridine (**7b**)

to (*E*)-methyl crotonate (**8b**) as a key step in a concise first asymmetric synthesis of the Celastraceae sesquiterpenoid constituent (–)-(1′*S*,2′*S*)-evoninic acid (**6s**). Given the synthetic/medicinal importance of pyridine-containing compounds and the paucity of pyridine conjugate addition reactions previously described, it is hoped that this methodology will find wide use in synthesis. Work is ongoing to apply the methodology to the synthesis of other 2- and 4-substituted pyridyl diacids⁵ found in macrodilactone Celastraceae sesquiterpenoids.

(17) The significant variation of the diastereoselectivity of this alkylation reaction as a function of the enolate counterion and solvent is noteworthy. Few similarly dependent alkylations and protonations have been reported: (a) Stork, G.; Boeckman, R. K. *J. Am. Chem. Soc.* **1973**, 95, 2016. (b) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, 67, 2885. (c) Hu, Y.; Bishop, R. L.; Luxemburger, A.; Dong, S.; Paquette, L. A. *Org. Lett.* **2006**, 8, 2735.

(18) The following hydrolyses were screened: pig liver esterase (PLE), immobilized PLE, lipase *P. cepacia*, lipase *P. fluorescens*, *Candida antactica* lipase B (Novozym-435), and α -chymotrypsin.

(19) As determined by conversion to its (*R*)- α -methylbenzylamide derivative using Mukiyama's coupling reagent and comparison of its ¹H NMR spectrum with that of a 1:1 mixture of diastereoisomers obtained likewise from acid (\pm)-**10s** (see Supporting Information).

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Supporting Information Available: Experimental procedures and full characterization for compounds **5–10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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