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Total Synthesis of (+)-Lithospermic Acid by Asymmetric Intramolecular Alkylation via Catalytic C−H Bond Activation

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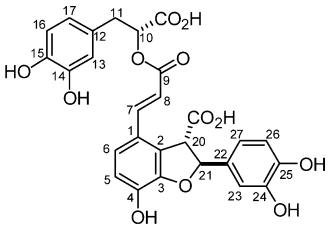
(+)-Lithospermic acid (+)-(**1**)[1] has recently attracted considerable interest due to its reported potent and nontoxic anti-HIV activity that results from inhibition of HIV-1 integrase,[2] which is an intensively studied therapeutic target for the treatment of AIDS. Though several groups have isolated (+)-lithospermic acid to study its biological activity, its synthesis has not yet been reported. Herein we report the first total synthesis of (+)-lithospermic acid using asymmetric intramolecular alkylation via rhodium-catalyzed C−H bond activation. The synthesis further provides the first example of employing a chiral nonracemic imine as a directing group in a C−H bond activation method.

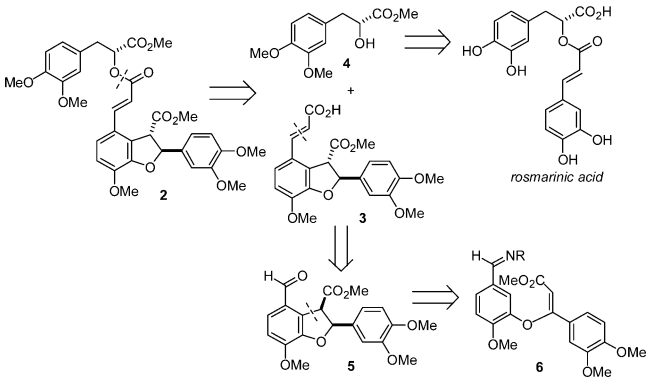
The densely functionalized dihydrobenzofuran core of (+)-**1** provides a formidable test of our recently developed method for intramolecular alkylation via directed C−H bond activation.[3] The polyphenolic nature of (+)-lithospermic acid represents a further synthetic challenge in that it requires an appropriate protecting group strategy that allows late-stage global deprotection in the presence of the labile C-9 ester and C-21 benzylic ether functional groups.



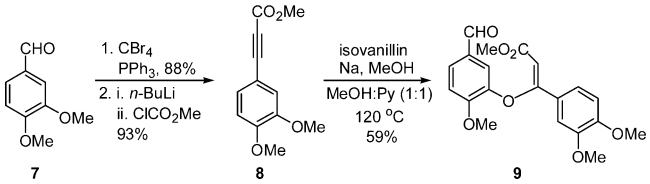
(+)-1

We envisioned that global deprotection of heptamethyl lithospermic acid **2** would provide the most efficient route to (+)-lithospermic acid (Scheme 1). Ester **2** could be prepared from acid **3** and alcohol **4**, which can be made in two steps from commercially available rosmarinic acid. Cinnamic acid **3** can be prepared by a Knovenagel condensation and epimerization of dihydrobenzofuran **5**. Using intramolecular alkylation via catalytic C−H bond activation, **5** should be accessible from imine **6**, which would constitute the first application of our C−H activation chemistry to natural product synthesis.[4,5]

Scheme 1. Retrosynthesis of (+)-Lithospermic Acid

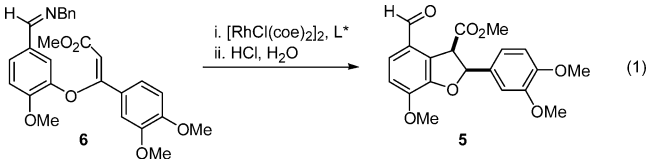


Scheme 2. Synthesis of *Z* Olefin



Corey−Fuchs olefination of **7** followed by double elimination and trapping with methyl chloroformate provided ester **8** in excellent yield (Scheme 2). A conjugate addition reaction with isovanillin furnished **9**, with a 1:1 methanol and pyridine solvent mixture providing an optimized 3.2:1 ratio of *Z*:*E* isomers.[6] After chromatography and crystallization, the pure *Z* isomer was isolated in 59% yield.

Upon conversion of aldehyde **9** to imine **6**, the rhodium-catalyzed intramolecular alkylation was next investigated (eq 1). Using ferrocenyl−PCy_2 ($FcPCy_2$) as the ligand, dihydrobenzofuran **5** was isolated solely as the cis isomer in 89% overall yield. This example constitutes, by far, the most densely functionalized system to which this C−H activation method has been applied.



(1)

Unfortunately, chiral catalysts could not be identified that provided satisfactory yields and/or enantioselectivities in this cyclization. An alternative approach to inducing chirality in the reaction involves using chiral amine auxiliaries to yield a diastereoselective insertion of the prochiral olefin. Thus, a variety of chiral nonracemic amines were screened in this reaction (Table 1). Chiral benzylic amines proved to be the most effective (entries 1, 2, 5, and 6), with aminoindane **16** giving the best results, generating the cyclization product in 63% yield and 76% ee after auxiliary hydrolysis (entry 6). An increase in catalyst loading and reaction time further improved the yield of the reaction without significantly eroding the asymmetric induction (entry 7), while decreasing the temperature was found to improve the selectivity but reduce the yield significantly (entry 8). Thus, imine formation of **9** with (*R*)-(−)-aminoindane followed by cyclization proceeded cleanly to give, after hydrolysis, dihydrobenzofuran **5** in 88% yield with 73% ee. Recrystallization of the product from benzene/pentane mixtures provided the product in 56% yield as a single enantiomer. X-ray structure analysis of a hydrazone derivative of **5** unambiguously established the sense of induction in the cyclization reaction (see Supporting Information).

Knovenagel condensation of **5** not only converted the aldehyde to the desired cinnamic acid but also epimerized the C-20 position to give the desired thermodynamically more stable *anti* diastereomer

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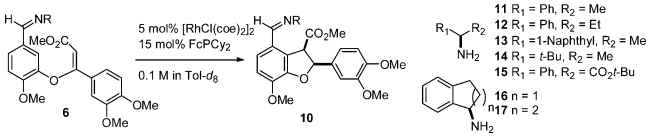
Table 1. Asymmetric Cyclization Using Chiral Imines



entry	RNH_2	T (°C)	t (h)	% Rh	% $FcPCy_2$	% **10**[a]	% ee[b]
1	**11**	75	6	5	15	53	48
2	**12**	75	4	5	15	68	50
3	**13**	75	22	5	15	<10	18
4	**14**	75	24	5	15	0	
5	**15**	75	4	5	15	37	50
6	**16**	75	6	5	15	63	76
7	**16**	**75**	**20**	**10**	**30**	**88**[c]	**73**
8	**16**	50	20	5	15	31	80
9	**17**	75	20	5	15	3	nd

[a] Yields based on ^{1}H NMR integration relative to 2,6-dimethoxytoluene as an internal standard. [b] Enantiomeric excess determined after hydrolysis of **10** with 1 N HCl (aq) using chiral HPLC. [c] Isolated yield of the product after hydrolysis and column chromatography.

Scheme 3. Synthesis of Heptamethyl Lithospermic Acid

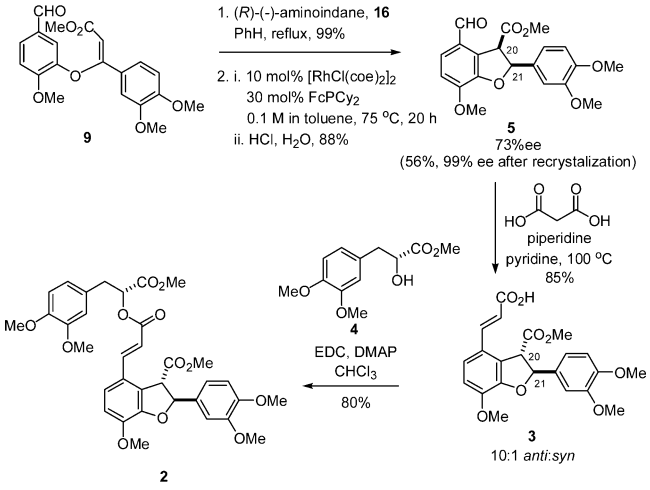
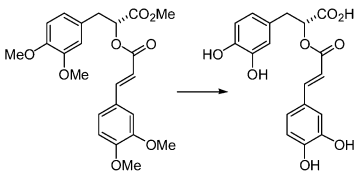


Table 2. Model Global Deprotection



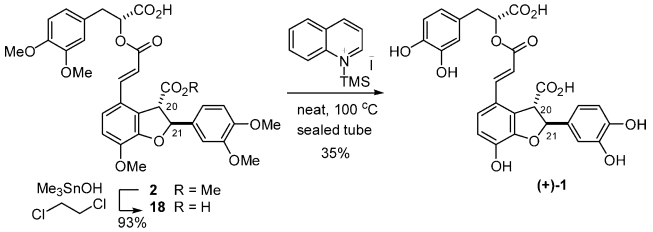
entry	reagent	% yield
1	BBr_3, CH_2Cl_2	ester cleavage
2	BBr_3·SMe_2	decomposition
3	NaCN, DMSO	decomposition
4	EtSNa, DMF	ester cleavage
5	$AlBr_3$, EtSH, PhH	decomposition
6	TMSI, $CHCl_3$	<10
7	**TMSI, quinoline**	**57**

as the major product in 85% yield (Scheme 3).[7,8] Esterification of **3** with alcohol **4** was accomplished with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) and 4-(dimethylamino)pyridine (DMAP) to provide heptamethyl lithospermic acid **2** in 80% yield.

Completion of the synthesis required removal of five ether and two ester methyl groups to arrive at (+)-lithospermic acid. To model this final reaction, the deprotection of pentamethyl rosmarinic acid was studied, and it was found that numerous conditions gave only decomposition products (Table 2). Using Brossi's conditions,[9] in which iodotrimethylsilane (TMSI) and quinoline are precomplexed, pentamethyl rosmarinic acid was converted back to rosmarinic acid in 57% yield (entry 7).

Unfortunately, final deprotection of **2** using the TMSI/quinoline conditions led only to decomposition of the starting material. Ring opening of the dihydrobenzofuran through β-elimination of the C-21 phenoxy group proved to be a major decomposition pathway. This could be minimized, however, by converting the C-20 methyl ester

Scheme 4. Completion of the Synthesis of (+)-Lithospermic Acid



to the corresponding acid. Although standard saponification conditions did not result in selective hydrolysis of the two methyl esters over the C-9 ester linkage, diacid **18** could be obtained in excellent yield by employing a recently reported protocol for the hydrolysis of methyl esters[10] using Me_3SnOH (Scheme 4). Subsequent treatment of this diacid with sublimed TMSI quinoline adduct resulted in removal of the five ether methyl groups to provide (+)-lithospermic acid in 35% yield.

In summary, an efficient, asymmetric synthesis of (+)-lithospermic acid was accomplished in 10 steps and 5.9% overall yield. The asymmetric intramolecular alkylation to provide **5** is the first example of chiral imine-directed C−H bond activation and represents the first application of our C−H activation method to natural product synthesis. Due to this efficient synthesis, the preparation of lithospermic acid analogues for evaluation as HIV-1 integrase inhibitors is also in progress.

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Supporting Information Available: Complete experimental details and spectral data for all compounds described (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For use of our method to the synthesis of a drug candidate, see 3b.
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