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COMMUNICATIONS

Published on Web 08/04/2006

Toward the Development of a General Chiral Auxiliary. Enantioselective Alkylation and a New Catalytic Asymmetric Addition of Silyloxyfurans: Application to a Total Synthesis of (−)-Rasfonin

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In 2000, TT-1, an α-pyranone-containing natural product, was isolated by Ishibashi et al. from the fungus *Trichurus terrophilus*.[1] In the same year, Hayakawa and co-workers reported the isolation of (−)-rasfonin from the fermented mycelium of *Taleromyces* species 3656-A1.[2] Through chemical and spectroscopic studies,[1,2] TT-1 and (−)-rasfonin (**1**) were found to be identical and to possess the depicted structure and absolute configuration consisting of two principal alkyl appendages and a δ-lactone core.

(−)-Rasfonin (**1**) was named after the protein *ras* since its biological activity is elicited in cells that are dependent on *ras* for growth. The protein *ras* functions as a molecular switch for signal transduction pathways that control cell growth and differentiation, as a stimulant for cell growth, as a suppressor of apoptosis (programmed cell death), and, most significantly, as an oncogene that is able to induce tumors in animals or cell cultures.[2]

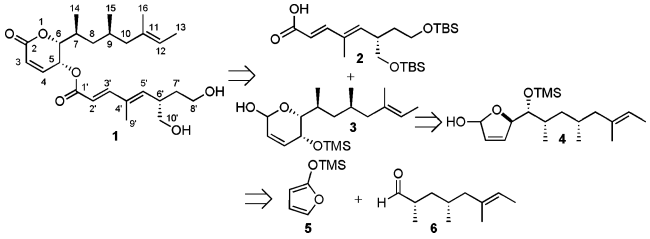
Recent studies have indicated that (−)-rasfonin (**1**) can selectively destroy *ras*-dependent cells with an IC_{50} of 0.16 μg/mL.[2] Exposure to higher concentrations of (−)-**1** (1 μg/mL) resulted in a considerable number of cells exhibiting condensed chromatin and fragmented nuclei, the typical markers of apoptosis.[2] A non-*ras*-dependent cell line was unaffected at concentrations of (−)-**1** up to 1.25 μg/mL.

Selective inducers of apoptosis in *ras*-dependent cells could represent a novel class of cancer chemotherapeutics useful for treatment of tumors expressing constitutively active, mutant *ras*. Despite this potential, only one lengthy total synthesis of (−)-**1** has been reported.[3] That synthesis was principally intended to confirm the structure and absolute configuration of (−)-**1**. Thus, we sought to develop an alternative route to (−)-**1** that would be flexible enough for analogue preparation and more amenable to scale-up.

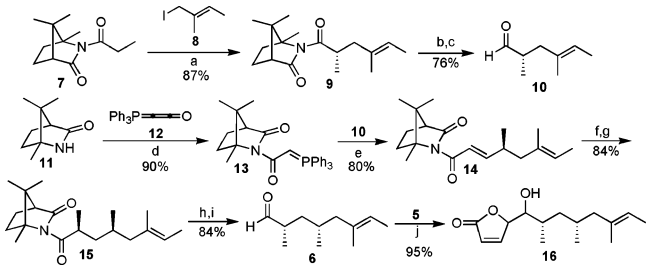
In our retrosynthetic analysis, (−)-**1** was envisioned to be derived from diene acid **2** and pyranol **3** (Scheme 1). Rearrangement of furanol **4** with concomitant [1,4]-silyl transfer would afford intermediate **3**. An asymmetric vinylogous Mukaiyama aldol addition[4] of siloxyfuran **5** to aldehyde **6** would give rise to the butenolide precursor to furanol **4**. Judicious use of the appropriate enantiomers of the camphor lactam chiral auxiliaries should, in theory, allow access to all stereoisomers of the two side chains in high enantiomeric purity via the same reaction sequence for each.

Diastereoselective alkylation of (1*S*)-2-azaimide **7** (Scheme 2) with tiglic iodide (**8**) afforded alkenyl imide **9** in 87% yield as a single diastereomer.[5] Reductive removal of the camphor lactam and subsequent Swern oxidation[6] furnished the sensitive aldehyde **10**. Homologation of **10** with phosphorane **13**,[7] in turn obtained in 90% yield by acylation of (1*R*)-**11** with (triphenylphosphoranylidene)ketene,[8] provided imide **14** in 80% yield with >95:5 *E*:*Z* diastereoselectivity. No detectable epimerization of the proximal stereogenic center was observed.

Scheme 1. Retrosynthetic Analysis



Scheme 2. Preparation of Butenolide **16**[a]



[a] Reagents and conditions: (a) LiHMDS, THF, 0 °C, then **8**, −40 °C, 18 h; (b) $LiBH_4$, MeOH, Et_2O, 0 °C to rt, 2 h; (c) $(COCl)_2$, DMSO, TEA, −78 to 0 °C, 45 min; (d) toluene, reflux, 24 h; (e) DCE, 70 °C, 18 h; (f) Et_3SiH, $Pd/CaCO_3/PbO$, acetone, 50 °C, 18 h; (g) LiHMDS, THF, −78 °C, then MeI, −78 to −40 °C, 18 h; (h) LAH, Et_2O, rt, 18 h; (i) NMO, TPAP, 4 Å MS, rt, 20 min; (j) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 18 h.

Regioselective reduction of the conjugated olefin in imide **14** with Lindlar catalyst and triethylsilane[9] followed by auxiliary-controlled diastereoselective methylation provided adduct **15** in 84% yield over two steps and >95:5 dr. Reductive removal of the auxiliary, followed by Ley oxidation,[10] afforded aldehyde **6** with complete retention of stereochemical fidelity.

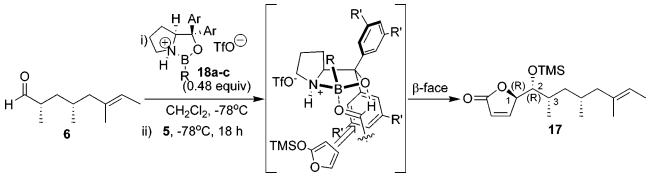
The pivotal vinylogous Mukaiyama aldol addition was first attempted using $BF_3{\cdot}OEt_2$. Reaction of **5** and **6** afforded butenolide product **16** in 95% yield with 11.7:1 *threo*:*erythro* diastereoselectivity. The (R,R)-threo:(S,S)-threo diastereomeric ratio was only 1.3:1, verifying the expected lack of substrate control of diastereofacial selectivity in addition to the aldehyde.

Considering the excellent *threo:erythro* relative diastereoselectivity provided by $BF_3{\cdot}OEt_2$, we envisioned use of a chiral boron Lewis acid for the requisite Mukaiyama aldol reaction. The chiral cationic oxazaborolidines used by Corey for asymmetric Diels−Alder reactions appeared attractive.[11] The easy preparation and modification and high reactivity of these catalysts rendered them promising candidates for catalysis of the key vinylogous Mukaiyama aldol reaction.[12]

Our results (Table 1) are in accord with Corey's report.[11] Increasing the steric bulk of the boron substituent (**18a** → **18b**) led to significantly higher asymmetric induction. Utilization of the

10.1021/ja063532+ CCC: $33.50

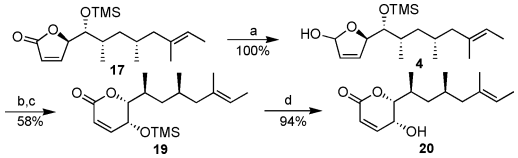
Table 1. Catalysis of the Vinylogous Mukaiyama Aldol by **18**



entry	**18**	R	R′	yield (%)	*threo*:*erythro*[a]	*threo* dr[a]
1	**a**	Me	H	75	4:1	3:1
2	**b**	*o*-tol	H	78	11:1	6:1
3	**c**	*o*-tol	Me	81	20:1	>20:1

[a] Diastereomeric ratio was measured by ^{1}H NMR.

Scheme 3. Synthesis of Pyranone **20**[a]



[a] Reagents and conditions: (a) DIBAL-H, Et_2O, −78 °C, 10 min; (b) DBU, THF, 0 °C, 20 h; (c) MnO_2, CH_2Cl_2, rt, 24 h; (d) 1 N HCl, THF, rt, 25 min.

more-hindered oxazaborolidine **18c** afforded butenolide **17** in 81% yield with 20:1 *threo*:*erythro* relative diastereoselectivity. To our delight, the (*R*,*R*)-*threo*:(*S*,*S*)-*threo* diastereomeric ratio exceeded 20:1. A putative transition state (Table 1) based on Corey's model[11] for association of the aldehyde with **18a**−**c** suggests that the B-substituent controls orientation of the siloxyfuran (*erythro*:*threo* or C_1−C_2 diastereoselection), and the bulky ring aryl groups control the alkyl group orientation of the aldehyde (C_2−C_3 diastereoselection).

Reduction of **17** with DIBAL-H furnished lactol **4** quantitatively (Scheme 3). Sequential treatment of **4** with DBU and oxidation gave an equilibrium mixture (1:1) of **17** and **19**. Recycling recovered **17** afforded **19** in 58% overall yield. Desilylation then provided alcohol **20** in 94% yield.

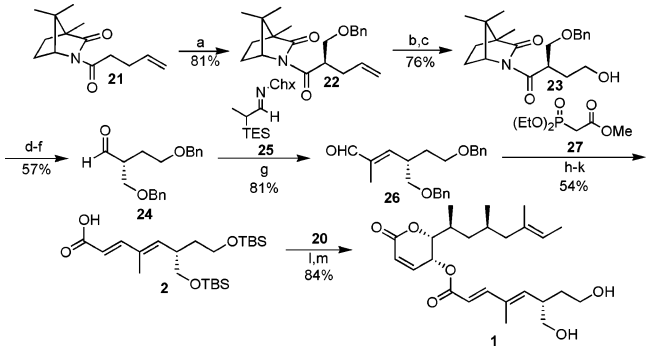
The key chiral center in diene acid **2** was installed via a $TiCl_4$-catalyzed asymmetric alkylation of 3-azaimide **21** with BOMCl (Scheme 4), providing **22** in 81% yield and >95:5 diastereoselectivity.[13] Terminal olefin cleavage by ozonolysis/BH_3·THF reduction furnished imido alcohol **23** in 76% overall yield. After protection of the alcohol as the benzyl ether, **23** was transformed by standard methods to aldehyde **24** (Scheme 2), whose remarkable base sensitivity led to difficulties in homologation to enal **26**. Ultimately, conversion was achieved with no decomposition of **24** using a modified Corey−Peterson protocol.[14] Condensation of **24** with lithiated α-silyl imine **25** followed by TFA-induced isomerization[15] provided (*E*)-**26** (50:1) in 81% yield after in situ hydrolysis of the intermediate iminium ion(s).

Horner−Wadsworth−Emmons olefination[16] of aldehyde **26** with methyl diethylphosphonoacetate (**27**) furnished the corresponding dienoate in 96% yield as a single diastereomer. The diene ester was then elaborated to target acid **2** by protecting group modification and hydrolysis (56% over three steps).

The complete carbon skeleton of (−)-rasfonin (**1**) was assembled via Yamaguchi coupling of alcohol **20** with diene acid **2**.[17] Desilylation with CSA afforded (−)-rasfonin (**1**) in 84% yield.[1−3]

The present total synthesis is shorter (longest linear sequence of 16 steps) and higher yielding (12.7% overall yield) than the only reported route.[3] The flexibility of camphor lactams as auxiliaries was exemplified during the installation of the side chain stereogenic

Scheme 4. Completion of the Total Synthesis of (−)-Rasfonin (**1**)[a]



[a] Reagents and conditions: (a) $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C, then BOMCl, 0 °C, 24−48 h; (b) O_3, CH_2Cl_2:MeOH (95:5), pH 7 phosphate buffer, −78 °C, then DMS, −78 to rt, 18 h; (c) BH_3·THF, THF, 0 °C, 2.5 h; (d) (MeO)(Me)NH·HCl, $AlMe_3$, THF, −78 to 0 °C, 1.5 h; (e) BnBr, TBAI, Ag_2O, CH_2Cl_2, rt, 4 h; (f) DIBAL-H, Et_2O, −78 °C, 3 h; (g) *s*-BuLi, THF, −78 to −20 °C, 1 h, aq. workup, then TFA, THF, 0 °C, 1 h, then H_2O, 18 h; (h) *n*-BuLi, THF, 0 °C to rt, 18 h; (i) BCl_3·DMS, CH_2Cl_2, −78 °C to rt, 1 h; (j) TBSCl, imidazole, CH_2Cl_2, rt, 18 h; (k) LiOH·H_2O, THF, H_2O, MeOH, rt, 40 h; (l) 2,4,6-trichlorobenzoyl chloride, TEA, toluene, rt, 1 h, then **20**, toluene, DMAP, rt, 5 h; (m) CSA, CH_2Cl_2, MeOH, 0 °C, 2 h.

centers via asymmetric alkylation. To the best of our knowledge, we report the first use of cationic chiral oxazaborolidine catalyst **18c** in the key assembly of butenolide **17** via an asymmetric vinylogous Mukaiyama aldol addition, whose scope we are currently seeking to expand.

Acknowledgment. We thank the National Science Foundation (CHE-0305790) for support of these studies.

Supporting Information Available: Experimental procedures and analytical and spectroscopic (^{1}H NMR, ^{13}C NMR, IR) data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA063532+