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Enantioselective Nazarov Cyclization Catalyzed by a Cinchona Alkaloid Derivative

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Abstract

Nucleophilic catalysts for a 1,6 addition/Nazarov cyclization/elimination sequence were evaluated for their ability to induce enantioselectivity in the electrocyclization step. Of the tertiary amines examined, it was found that a cinchona alkaloid derivative was able to generate substituted 5-hydroxy γ -methylene cyclopentenones with excellent enantioselectivity. The study results suggest that successful cyclization depends upon the ability of the dienyl diketone substrate to readily adopt an *s-cis* conformation.

Keywords

Nazarov cyclization; enantioselective; cinchona alkaloid

Introduction

5-hydroxycyclopentenones are an important motif in natural products and other valuable small molecules. For example, stemonamide¹ is isolated from Stemonaceae that are used in Chinese and Japanese medicine for cough relief,² phorbol³ has tumor-promoting activity through the activation of protein kinase C,⁴ and przewalskin B⁵ has weak anti-HIV-1 activity (Figure 1).

One method for the synthesis of substituted cyclopentenones is the Nazarov cationic electrocyclization, which is often initiated by activation of a carbonyl group, with either protic acid or Lewis acid.⁶ It has become possible, using acid catalysis, to achieve enantioselective cyclizations of divinyl ketone derivatives.⁷ In addition to these achievements, alternative methods for generating pentadienyl cation intermediates have become increasingly common,^{6f} expanding the utility and convenience of the Nazarov cyclization as a synthetic strategy. In ongoing studies, we have developed a Nazarov cyclization variant that is initiated the 1,6 conjugate addition of a nucleophile to a dienyl diketone.⁸ In these reactions, various neutral nucleophiles (such as malonate derivatives,

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primary, and secondary amines)⁸ and anionic nucleophiles (sodium alkoxide and sodium thiolate)⁹ are effective promoters, generating 5-hydroxycyclopentenones **2** with excellent diastereoselectivity (eq 1). In addition, tertiary amines initiate either the addition-elimination process (eq 2) or a 6π electrocyclic reaction (eq 3) to afford methylene cyclopentenones **3** and 2*H*-pyrans **4**.⁹

(1) (2) (3)

Herein, we describe an asymmetric version of the addition/electrocyclization/elimination, catalyzed by a cinchona alkaloid derivative. The sequence generates 5-hydroxycyclopentenones (cf. equation 2 and Figure 1) in enantioenriched form.

The mechanism proposed for the equation 2 cyclization inspired our experimental design. As shown in Scheme 1, addition of a tertiary amine to **5** in a 1,6-fashion, followed by single bond rotation, is thought to generate intermediate **7**. The 4π electrocyclization of **7**, followed by elimination of the tertiary amine, then furnishes the γ -methylene cyclopentenone **3**. This reaction sequence is similar to the Morita-Baylis-Hillman reaction¹⁰ and the Rauhut-Currier reaction¹¹. Enantioselective versions of these two reactions have been achieved with the use of cinchona alkaloids¹² and a chiral guanidine¹³. We sought to examine these catalysts in the 1,6-conjugate addition sequence, to evaluate whether they could effect the enantioselective 4π electrocyclization of intermediate **7**.

Results and Discussion

In the screen of different tertiary amines, we found that either catalytic or stoichiometric amount of tetramethyl guanidine (TM-guanidine) led us to **11** (Table 1, entry 1 and entry 2). The reaction with a stoichiometric amount of DABCO allowed us to obtain the product **11** in 93% yield (entry 3). While trying to use quinidine, no reaction was observed (entry 4 and entry 5). In the attempt of using N-methylephedrine (**12**), low enantioselectivity was observed (entry 6–8). Fortunately, with Hatakeyama's chiral cinchona alkaloid **13**, 88:12 er

was obtained with 74% yield with 86% conversion of starting material in 43 h (entry 9).¹² Hatakeyama and coworkers hypothesize that the enhanced reactivity of **13** relative to quinidine can be attributed to the reduced steric demand around the nucleophilic tertiary nitrogen atom, and that the phenol group of **13** serves as a Brønsted acid. Upon screening different temperatures, we found the enantioselectivity was not affected by increasing temperature to 50 °C which increased the rate of the reaction from 43h to 20h (entry 10). We increased the enantioselectivity up to 97:3 er when the reaction run at –20 °C, however, this also decreased the rate of the reaction (entry 12). In addition, changing the solvent from THF to DMF dramatically decreased the reaction time and optimized the enantioselectivity to 99:1 er (entry 15). We could reduce the catalyst loading to 3 mol % with excellent selectivity (entry 15–18).

With optimized conditions in hand, we began to examine the substrate scope. We were pleased to find that both electron-withdrawing and electron-donating aryl substituents are tolerated in the addition/electrocyclization/elimination reaction (Table 2, entry 1–3), as well as heteroaromatic substituents (entry 4 and entry 5). High enantiomeric ratios were obtained in all cases. When the R² substituent was either cyclohexyl or trimethylsilyl (TMS), we also obtained the desired products with excellent enantioselectivities (entry 6 and entry 7). Interestingly, when the R² substituent was either an alkyl group (butyl, entry 8) or hydrogen (entry 9), only trace amounts of product was formed before decomposition of the substrate occurred. Experiments using malonate as nucleophile did not produce enantioenriched products.

As shown in Table 2, it was not possible to promote cyclization of substrate **20** (R² = *n*-butyl). Based on these results, we surmise that successful conjugate addition/electrocyclization depends upon the steric influence of the R² group: it must be large enough to promote isomerization to the *s-trans* conformer, which is required to undergo the 4π electrocyclization (eq 4).

(4)

In conclusion, we have described a highly enantioselective 1,6 addition/Nazarov cyclization/elimination reaction catalyzed by cinchona alkaloid derivative **13**. In the course of screening substrates, we also found the size of R² is critical to the efficiency of the reaction sequence. Further investigations are underway, including asymmetric 1,6-conjugate addition initiated Nazarov reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Ye Y, Qin GW, Xu RS. *J Nat Prod.* 1994; 57:665–669.
2. (a) Aloise Pilli R, da Conceicao Ferreira de Oliveria M. *Natural Product Reports.* 2000; 17:117–127. [PubMed: 10714902] (b) Alibés R, Figueredo M. *Eur J Org Chem.* 2009; 2009:2421–2435.
3. Okuda T, Yoshida T, Koike S, Toh N. *Phytochemistry.* 1975; 14:509–515.
4. Hirota M, Suguri H, Endo Y, Shudo K, Wongchai V, Hecker E, Fujiki H. *Cancer Research.* 1988; 48:5800–5804. [PubMed: 3167837]
5. Xu G, Hou AJ, Zheng YT, Zhao Y, Li XL, Peng LY, Zhao QS. *Org Lett.* 2007; 9:291–293. [PubMed: 17217287]
6. For recent reviews on the Nazarov cyclization, see: Nakanishi W, West FG. *Curr Opin Drug Discov.* 2009; 12:732–751. Grant TN, Rieder CJ, West FG. *Chem Commun.* 2009:5676–5688. Davis RL, Tantillo DJ. *Curr Org Chem.* 2010; 14:1561–1577. Vaidya T, Eisenberg R, Frontier AJ. *ChemCatChem.* 2011; 3:1531–1548. Shimada N, Stewart C, Tius MA. *Tetrahedron.* 2011; 67:5851–5870. [PubMed: 21857751] Spencer WT III, Vaidya T, Frontier AJ. *Eur J Org Chem.* 2013:3621–3633. Tius MA. *Chem Soc Rev.* 2014; 43:2979–3002. [PubMed: 24196585] Di Grandi MJ. *Org Biomol Chem.* 2014; 12:5331–5345. [PubMed: 24947937]
7. (a) Aggarwal VK, Belfield AJ. *Org Lett.* 2003; 5:5075. [PubMed: 14682768] (b) Liang G, Gradl N, Trauner D. *Org Lett.* 2003; 5:4931. [PubMed: 14682732] (c) Liang G, Trauner D. *J Am Chem Soc.* 2004; 126:9544. [PubMed: 15291550] (d) Nie J, Zhu HW, Cui H, Hua M, Ma J. *Org Lett.* 2007; 9:3053. [PubMed: 17629286] (e) Rueping M, Ieawsuwan W, Antonchick AP, Nachtsheim BJ. *Angew Chem, Int Ed.* 2007; 46:2097. (f) Walz I, Togni A. *Chem Commun.* 2008:4315. (g) Yaji K, Shindo M. *Synlett.* 2009:2524. (h) Rueping M, Ieawsuwan W. *Adv Synth Cat.* 2009; 351:78. (i) Kawatsura M, Kajita K, Hayase S, Itoh T. *Synlett.* 2010:1243. (j) Cao P, Deng C, Zhou Y, Sun X, Zheng J, Xie Z, Tang Y. *Angew Chem, Int Ed.* 2010; 49:4463. (k) Bow WF, Basak AK, Jolit A, Vicic DA, Tius MA. *Org Lett.* 2010; 12:440. [PubMed: 20030316] (l) Basak AK, Shimada N, Bow WF, Vicic DA, Tius MA. *J Am Chem Soc.* 2010; 132:8266. [PubMed: 20507121] (m) Rueping M, Ieawsuwan W. *Chem Commun.* 2011:11450. (n) Hutson GE, Türkmen YE, Viresh H, Rawal VH. *J Am Chem Soc.* 2013; 135:4988–4991. [PubMed: 23506509]
8. (a) Brooks JL, Caruana PA, Frontier AJ. *J Am Chem Soc.* 2011; 133:12454–12457. [PubMed: 21780785] (b) Brooks JL, Frontier AJ. *J Am Chem Soc.* 2012; 134:16551–16553. [PubMed: 23004564] Brooks JL, Frontier AJ. *J Am Chem Soc.* 2013; 135:19362. (correction). (c) Brooks JL, Huang YW, Frontier AJ. *Org Syn.* 2014; 91:93–105.
9. Jacob SD, Brooks JL, Frontier AJ. *J Org Chem.* 2014; 79:10296–10302. [PubMed: 25325706]
10. For recent reviews on the Morita-Baylis-Hillman reaction, see: Shi YL, Shi M. *Eur J Org Chem.* 2007:2095. Masson G, Housseman C, Zhu J. *Angew Chem Int Ed.* 2007; 46:4614. Basavaiah D, Venkateswara Rao KV, Reddy RJ. *Chem Soc Rev.* 2007; 36:1581. [PubMed: 17721583] Singh V, Batra S. *Tetrahedron.* 2008; 64:4511. Declerck V, Martinez J, Lamaty F. *Chem Rev.* 2009; 109:1. [PubMed: 19140772] Carrasco-Sanchez V, Simirgiotis MJ, Santos LS. *Molecules.* 2009; 14:3989. [PubMed: 19924044] Basavaiah D, Reddy BS, Badsara SS. *Chem Rev.* 2010; 110:5447. [PubMed: 20735052] Wei Y, Shi M. *Acc Chem Res.* 2010; 43:1005. [PubMed: 20232829] Mansilla J, Saa JM. *Molecules.* 2010; 15:709. [PubMed: 20335941] Lu Y, Wang SX, Han X, Zhong F, Wang Y. *Synlett.* 2011:2766. Basavaiah D, Veeraraghavaiah G. *Chem Soc Rev.* 2012; 41:68. [PubMed: 21894342] Wei Y, Shi M. *Chem Rev.* 2013; 113:6659–6690. [PubMed: 23679920]
11. For a review on the Rauhut-Currier reaction, see: Aroyan CE, Dermenci A, Miller SJ. *Tetrahedron.* 2009; 65:4069–4084.
12. (a) Iwabuchi Y, Nakatani M, Yokoyama N, Hatakeyama S. *J Am Chem Soc.* 1999; 121:10219–10220. (b) Iwabuchi Y, Furukawa M, Esumi T, Hatakeyama S. *Chem Commun.* 2001:2030–2031. (c) Iwabuchi Y, Sugihara T, Esumi T, Hatakeyama S. *Tetrahedron Lett.* 2001; 42:7867–7871.

13. Terada M, Fukuchi S, Amagai K, Nakano M, Ube H. ChemCatChem. 2012; 4:963.
14. Typical procedure for the enantioselective Nazarov cyclization: A solution of corresponding dienyl diketone (50 mg, 0.17 mmol) in DMF (1.7 mL) in an oven dried round bottom flask was added to cinchona alkaloid **12** (1.6 mg, 0.0513 mmol). The reaction was allowed to stir at room temperature until the dienyl diketone was completely consumed. The solution was then diluted with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3×10 mL), the organic layers were then pooled and dried over MgSO_4 , filtered, and the solvent was removed under reduced pressure. The product was then purified by silica gel chromatography hexane-ethyl acetate as the eluent to give the methylene cyclopentenones **3**.

Figure 1.
Natural Products Bearing 5-hydroxycyclopentenones.

Scheme 1.
Proposed mechanism for the formation of **3**.

Table 1

Asymmetric Synthesis of Addition-elimination Product **11**.^a

entry	nucleophile (mol%)	solvent (0.1 M)	time	conversion (%)	yield (%)	e ^b
1	TM-guanidine (10)	THF	24h	100	47	-
2	TM-guanidine (130)	THF	2h	100	54	-
3 ^c	DABCO (100)	THF	2h	100	93	-
4	quinidine (10)	THF	-	-	-	-
5	quinidine (100)	THF	-	-	-	-
6	12 (10)	THF	-	-	-	-
7 ^d	12 (100)	THF	-	-	-	-
8 ^{d,e}	12 (100)	THF	24h	60	46	58:42
9	13 (10)	THF	43h	86	74	88:12
10 ^d	13 (10)	THF	20h	95	85	89:11
11 ^f	13 (10)	THF	-	-	-	-
12 ^g	13 (10)	THF	4d	82	73	97:3
13	13 (5)	THF	5d	80	74	90:10
14	13 (1)	THF	7d	77	19	85:15
15	13 (10)	DMF	1.5h	100	76	99:1
16	13 (5)	DMF	2.5h	100	80	99:1
17	13 (3)	DMF	4.5h	95	88	99:1
18	13 (1)	DMF	21h	86	52	97:3

^aReaction conditions were as described in the table.^bEnantioselectivities were determined by chiral Super-critical Fluid Chromatography (SFC).

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^c Reaction run at 80 °C.

^d Reaction run at 50 °C.

^e Y(OTf)₃ (1 mol%) and LiCl (2 equiv.) were used.

^f Reaction run at –78 °C.

^g Reaction run at –20 °C.

Table 2Scope of the Addition/Enantioselective cyclization/Elimination Reaction.^a

entry	temp. (°C)	time	product	yield(%)	er ^e
1	25	4.5h		88 ^b	99:1
2	25	20h		73	97:3
3	25	1h		98	>99:1
4	25	1.5h		97	97:3
5	25	8h		84	96:4

entry	temp. (°C)	time	product	yield(%)	er ^e
6	50	7d	 18	56	96:4
7	25	4h	 19	46 ^c	>99:1
8	-	-	 20	-	-
9	-	-	 21	-	-

^a Reaction Conditions: **5** (1 equiv.), **13** (3 mol%), DMF (0.1 M).

^b 5% starting material was recovered.

^c 38% of desilylated diethyl diketone was obtained.

^d A trace amount of product was observed when the temperature was elevated to 80 °C, using 10 mol% of Y(OTf)₃ and 2 equiv. of LiCl as additives for seven days.

^e Enantioselectivities were determined by chiral Super-critical Fluid Chromatography (SFC).