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A Reductive-Coupling plus Nazarov Cyclization Sequence in the Asymmetric Synthesis of Five-Membered Carbocycles

Daniel J. Kerr,[†] Jonathan M. White,[‡] and Bernard L. Flynn*,[†]

[†]*Medicinal Chemistry and Drug Action, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville Vic 3052, Australia, and* [‡]*Bio21 Institute, School of Chemistry, University of Melbourne, Parkville, VIC 3010, Australia*

bernard.flynn@pharm.monash.edu.au

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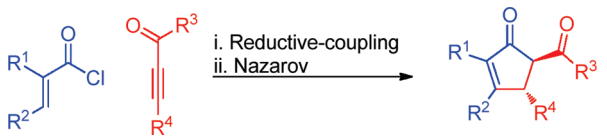


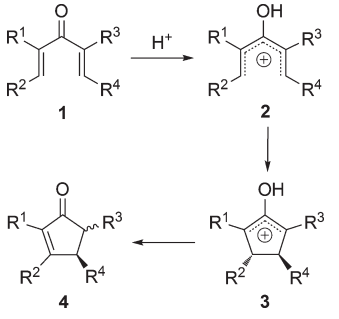
Palladium-mediated hydrostannylation of alkynoyl compounds is combined with Stille−Scott cross-coupling (reductive-coupling) to give one-pot access to divinyl and aryl vinyl ketones, which undergo Nazarov cyclization to give cyclopentenones upon treatment with acid. This reaction sequence has been studied with a variety of different substitution patterns, including the use of oxazolidinone auxiliaries to achieve torquoselectivity in the Nazarov cyclization. Through a combination of good yields and moderate to good levels of stereochemical induction, this approach affords efficient, convergent, and asymmetric access to a variety of different cyclopentanoid systems.

Introduction

The Nazarov cyclization has been known for more than 70 years and since its discovery has been undergoing continual refinement as an effective means of preparing 5-membered carbocycles.[1,2] The reaction involves protonation of a divinyl ketone **1** to give a pentadienyl cation **2**, which undergoes 4π-electrocyclization to give cyclopentenyl cation **3**, followed by proton elimination to give a cyclopentenone product **4** (Scheme 1).

Potentially, the Nazarov reaction could attain the synthetic utility for five-membered carbocycles that the Diels−Alder reaction enjoys for six-membered carbocycles, but further improvements are required in order to realize this equivalence. In particular, a key attribute of the Diels−Alder reaction is the ready availability of the substrates and the convergent, multibond forming nature of the (4 + 2)-cycloaddition. Such

SCHEME 1. Nazarov Reaction



versatile, convergent access to the divinyl ketone substrates **1** of the Nazarov reaction is still lacking. Also, while the application of chiral catalysts and auxiliaries is well established in the asymmetric Diels−Alder reaction, their application to the Nazarov reaction is still in its infancy and has a number of additional challenges.[3] A major limitation to the use of chiral acids in the enantioselective Nazarov reaction is the requirement to use significant amounts of acid, often greater than 1 equiv, in order to achieve cyclization. Only in cases where the reactivity of the substrate **1** is increased by appropriate use of electron-donating groups (EDGs) to stabilize **2** (one or more R groups = EDG) are catalytic levels of acid sufficient to achieve cyclization. Recent reports on the use of chiral

(1) For the first of Nazarov's publications in this area, see: Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. USSR, Ser. Khim.* **1941**, 211.

(2) For reviews of the Nazarov reactions, see: (a) Tius, M. *Eur. J. Org. Chem.* **2005**, 2193. (b) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (d) Harmata, M. *Chemtracts* **2004**, *17*, 416. (e) Habermas, K. L.; Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (f) Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1. (g) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: New York, 1991; Chapter 5.6.3, pp 751−784. (h) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (j) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Disc. Devel.* **2009**, *12*, 732.

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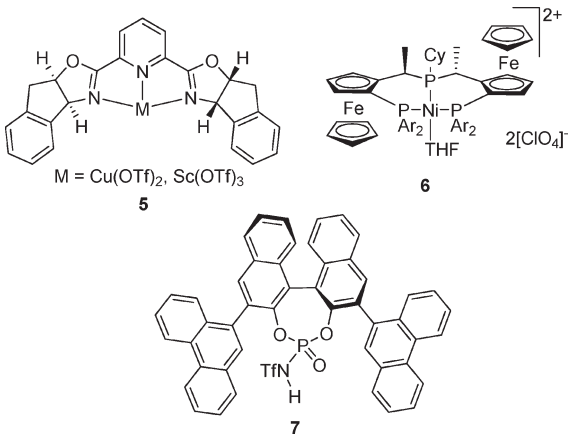
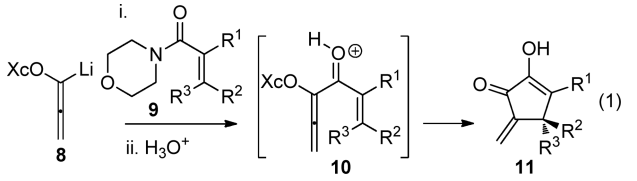
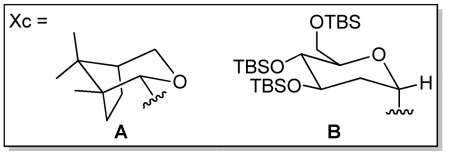
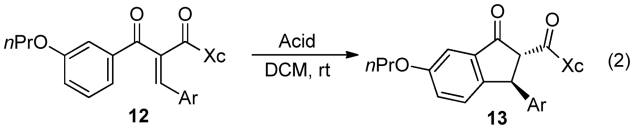


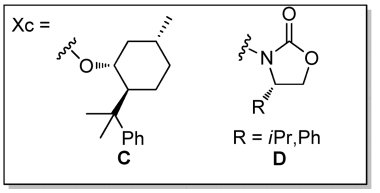
FIGURE 1. Chiral Acids.

Lewis acids have included the use of PYBOX·$Sc^{III}(OTf)_3$, PYBOX·$Cu^{II}(SbF_6)_2$ **5**,[3f,g] and PIGIPHOS·$Ni^{II}(ClO_4)_2$ **6**[3b] (Figure 1). In most cases, a 1:1 ratio of Lewis acid and substrate is employed producing enantiomeric excesses of 40−90%. Rueping and co-workers have achieved high levels of chiral induction (85−95% ee) using the chiral Brønsted acid (*N*-triflylphosphoramide) **7** when reactive dihydropyran substrates **1** (R^1,R^2 = dihydropyran) are used.[3b] In light of the requirement to use 1 equiv or more of acid to induce Nazarov cyclization in most cases, the direct attachment of the chiral auxiliary to the substrate and the use simple achiral acids to mediate the cyclization represents a suitable alternative to chiral acid promoted processes. In this respect, the Tius group has developed a convergent process for accessing Nazarov precursors that bear highly effective chiral auxiliaries (eq 1).[3a,c,e,f,k] Chiral allenic acetals **8** are lithiated and reacted with α,β-unsaturated amides **9**, giving highly reactive allenyl vinyl ketone intermediates **10** that undergo rapid in situ cyclization to the Nazarov product **11** in good enantiomeric excess (85−95% ee). The chiral auxiliary is detached during the Nazarov reaction, and the resultant formation of enol and methylidene substituents in the final product provide useful functionalities for further elaboration. This protocol represents a formal, enantioselective (3 + 2)-cycloaddition of allenic acetals **8** with α,β-unsaturated amides **9**. The synthetic utility of this approach to 5-memebered carbocycles has been demonstrated in the asymmetric synthesis of a number of complex molecular targets.[4] Another chiral auxiliary mediated asymmetric Nazarov reaction has been introduced by Pridgen and co-workers. This group has explored the use of 8-phenylmenthol and oxazolidinone auxiliaries attached through a carboxyl substituent, as in **12**, in the asymmetric Nazarov reaction to form indanones **13** (eq 2).[3h] Though few examples exist, this approach has considerable potential in providing asymmetric access to both indanones and cyclopentenones in a manner that accommodates a broader range of substitution patterns in the substrates and products than those attained using chiral catalysts and auxiliary bound allenol ethers. In this report, we describe a convergent preparation of divinyl ketones **1** that readily undergo Nazarov cyclization to give cyclopentenones **4**, in an alternative formal (3 + 2)-cycloaddition protocol to that developed by Tius and co-workers. The use oxazolidinone auxiliaries **1** [R^3 = C(O)oxazolidinone], as introduced by Prigden, has been extensively studied in the development of an asymmetric variant of this protocol.[5]









Results and Discussion

A one-pot, reductive-coupling procedure has been developed to provide convergent, stereoselective access to α,β-unsaturated carbonyl compounds **16** (Table 1). This process involves initial palladium-mediated *syn*-hydrostannylation of carboxyalkynes **14** to give a vinylstannane that then undergoes palladium-catalyzed cross-coupling (Stille) with a subsequently added organic halide **15**, giving trisubstituted alkenes **16**. Copper(I) chloride is added to facilitate the Stille cross-coupling reaction.[6] This one-pot reductive-coupling procedure affords stereo- and regioselective access to carboxyalkenes **16a**−**p** in good to excellent yields (Table 1). However, in some cases, the initially formed *Z*-isomers **16a**−**p** undergo thermal isomerism to give a mixture of *E*,*Z*-isomers.

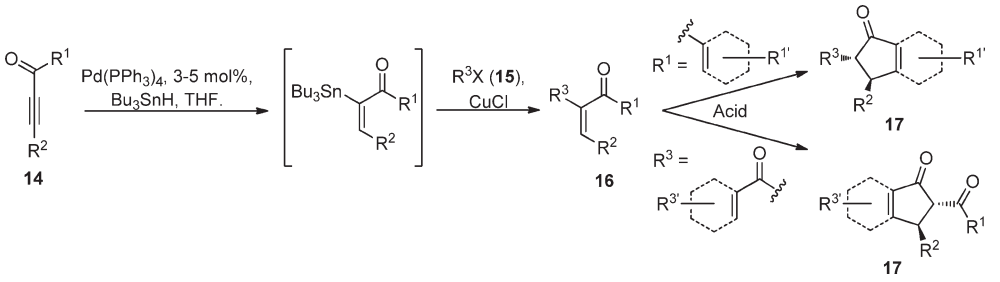
(3) (a) Banaag, A. R.; Tius, M. A. *J. Org. Chem.* **2008**, *73*, 8133. (b) Walz, I.; Togni, A. *Chem. Commun.* **2008**, 4315. (c) Dhoro, F.; Kristensen, T. E.; Stockman, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256. (d) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 2097. (e) delos Santos, D. B.; Banaag, A. R.; Tius, M. A. *Org. Lett.* **2006**, *8*, 2579. (f) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544. (g) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075. (h) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse, C.; Haltiwanger, R. C. *Synlett* **1999**, *9*, 1612. (i) Yaji, K.; Shindo, M *Synlett* **2009**, 2524. (j) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328. (k) During preparation of this manuscript, Tius and coworkers reported an asymmetric Nazarov cyclization of α-keto enones: Bow, W. F.; Basak, A. K; Jolit, A.; Vicic, D. A.; Tius, M. A. *Org. Lett.* **2010**, *12*, 440.

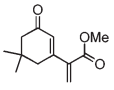
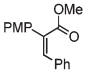
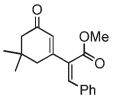
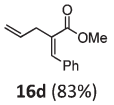
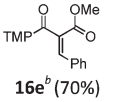
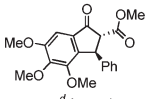
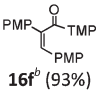
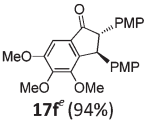
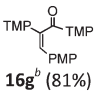
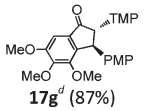
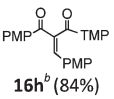
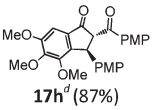
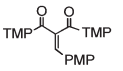
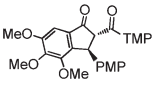
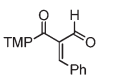
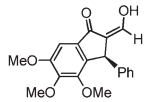
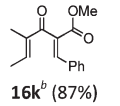
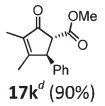
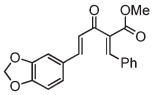
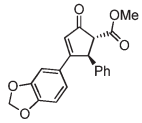
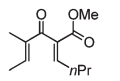
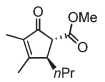
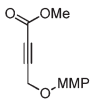
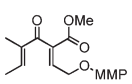
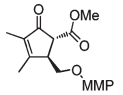
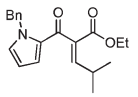
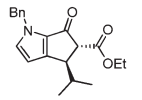
(4) (a) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123* (35), 8509. (b) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4* (20), 3363. (c) Berger, G. O.; Tius, M. A. *J. Org. Chem.* **2007**, *72* (17), 6473. (d) Wan, L.; Tius, M. A. *Org. Lett.* **2007**, *9* (4), 647.

(5) For a previous communication on elements of this work, see: Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380.

(6) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

TABLE 1. Reductive Coupling plus Nazarov Cyclization Sequence



Entry	14[a]	15[a]	16[a] (yield)	17[a,c] (yield)
1	 **14a**	 **15a**	 **16a** (61%)	-
2	 **14b**	PMP—I **15b**	 **16b** (75%)	-
3	**14b**	**15a**	 **16c**[c] (93%)	-
4	**14b**	 **15c**	 **16d** (83%)	-
5	**14b**	 **15d**	 **16e**[b] (70%)	 **17e**[d] (83%)
6	 **14c**	**15b**	 **16f**[b] (93%)	 **17f**[e] (94%)
7	**14c**	TMP—I **15e**	 **16g**[b] (81%)	 **17g**[d] (87%)
8	**14c**	 **15f**	 **16h**[b] (84%)	 **17h**[d] (87%)
9	**14c**	**15d**	 **16i** (81%)	 **17i**[d] (96%)
10	 **14d**	**15d**	 **16j** (48%)	 **17j**[d] (99%)
11	**14b**	 **15g**	 **16k**[b] (87%)	 **17k**[d] (90%)
12	**14b**	**15h**	 **16l**[b] (72%)	 **17l**[d,e] (0%)[8]
13	 **14e**	**15g**	 **16m**[b] (80%)	 **17m**[d] (88%)
14	 **14f**	**15g**	 **16n**[b] (85%)	 **17n**[e] (51%)
15	 **14g**	 **15i**	 **16o**[b] (82%)	 **17o**[d] (99%)
16	**14h**	**15j**	**16p** (not isolated)	**17p**[d,g] (73% from **14h**)

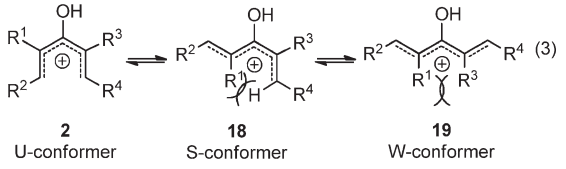
[a]PMP = *p*-methoxyphenyl, TMP = 3,4,5-trimethoxyphenyl, MMP = *m*-methoxyphenyl. [b]Initially formed as the kinetic product [(*Z*)-alkylidene isomer] but then slowly isomerizes to the thermodynamic mixture of double-bond isomers. [c]Acid 1−5 equiv in CH_2Cl_2, 18 °C, 1−16 h. [d]Acid = $MeSO_3H$. [e]Acid = $Cu(OTf)_2$. [g]Reductive coupling and Nazarov cyclization performed as a one-pot process in dichloromethane; see the main text.

When R^1 in **14** is an alkenyl or aryl group or R^3 in **15** is an α,β-unsaturated carbonyl group, the reductive-coupling procedure produces divinyl and aryl vinyl ketones **16e**−**p**. Nazarov cyclization of **16e**−**p** gives cyclopentanoids **17e**−**p** (entries 5−16, Table 1).[7] Most Nazarov reactions proceeded at room temperature or below upon treatment of **16** with 1−5 equiv of $MeSO_3H$ in dichloromethane. However, in the case of **16l**, only starting material was returned (entry 12, Table 1).

(7) This procedure has been used by us to prepare a series of permethoxylated chalcones and indanones for evaluation as tubulin polymerization inhibitors including examples **16f**−**i** and **17f**−**i**, amongst others: Kerr, D. J.; Hamel, E.; Jung, M. K.; Flynn, B. L. *Bioorg. Med. Chem.* **2007**, *15*, 3290.

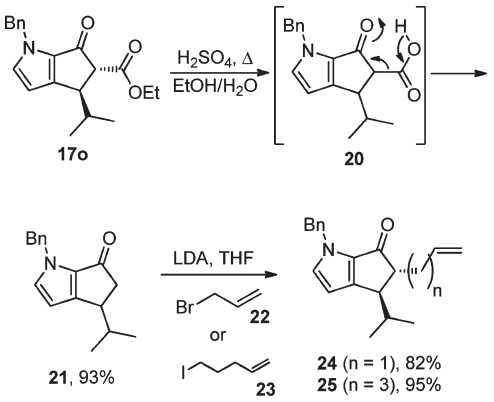
Further attempts to cyclize **16l** to give **17l** using more powerful acids and elevated temperatures failed, giving either the starting material **16l** or decomposition products.[8] A possible explanation for this relates to the effect that substitution patterns can have on the preferred conformations of the pentadienyl cation intermediate **2** (eq 3). The pentadienyl cation intermediate must adopt the periplanar U-conformation **2** in order to cyclize; however, other conformations of this cation are possible. Where R^1 in **2** is hydrogen, the S- and W-conformers, **18** and **19**, are of relatively low energy (little steric interference) and will be favored, but as R^1 is increased in size the reactive conformer **2** becomes more favored, increasing the reaction rate.[9] Treatment of **16n** with $MeSO_3H$ lead to significant decomposition and a very low yield of **17n** (not shown), but it could be cyclized to **17n** in reasonabe yield using the mild Lewis acid $Cu(OTf)_2$ (entry 14, Table 1).

In the case of **17p**, we combined both the reductive-coupling and the Nazarov cyclization into a one-pot process (entry 16, Table 1). Since the Nazarov cyclization is slower in THF, we used dichloromethane for the one-pot procedure and the more soluble copper(I) 2-thiophenecarboxylate (CuTC) instead of copper(I) chloride. Thus, to a solution of phenylpropynamide **14h** and $Pd(PPh_3)_4$ in dichloromethane the following reagents were added sequentially: tributyltin hydride (stir 0.5 h), **15j** and CuTC (stir 4.0 h), and $MeSO_3H$ (stir 1.0 h), giving **17p** in 73% yield.



The reductive-coupling process described above is an excellent method for preparing Nazarov precursors **1** where R^3 = carbonyl. This carbonyl plays a critical role in ensuring regio- and stereoselective access to Nazarov products **4** (R^3 = carbonyl). It directs the regiochemical placement of the double bond in **4** (R^3 = carbonyl) distal to the carbonyl, between R^1 and R^2.[2c,5] Additionally, the relative stereochemistry between R^3 and R^4 is controlled by the ready epimerization of the 1,3-dicarbonyl in **4** (R^3 = carbonyl) to give the thermodynamically more stable *trans*-product (Table 1). These carbonyls are also excellent substituents for further elaboration and, in the case of esters, can be completely removed by hydrolysis and decarboxylation and replaced by other substituents by α-substitution of the ketone. For example, acid hydrolysis of ester **17o** gives **20**, which readily decarboxylates to give **21** (93%) (Scheme 2). Alkylation of **21** using LDA and alkyl halides **22** and **23** gives **24** (82%) and **25** (95%), respectively, as single diastereomers (Scheme 2). In addition to the above, the R^3 group in **4** (R^3 = carbonyl) can also serve a labile linker to a chiral auxiliary. As initially demonstrated by Pridgen, oxazolidinones are potentially useful auxiliaries

SCHEME 2. Ester Substitution



for linking to this carbonyl and inducing torquoselectivity in the Nazarov reaction (eq 2).[3h] Pridgen and co-workers only examined a few examples of this reaction and focused solely on indanones. In the further development the reductive-coupling plus Nazarov cyclization procedure as a method for preparing chiral cyclopentanoids, we have undertaken a more extensive examination of the potential of oxazolidinones in torquoselective Nazarov reactions.

For the purpose of our evaluation of different oxazolidinone auxiliaries, we developed a facile one-pot method for the construction of various *N*-alkynoyloxazolidinones **29** from terminal alkynes **26** (Table 2). Deprotonation of terminal alkyne **26** with *n*-BuLi and reaction with carbon dioxide gives a lithium carboxylate (not shown) that is converted to the mixed pivaloyl anhydride **27** upon reaction with pivaloyl chloride. Anhydride **27** is not isolated but reacted directly with the lithium salt of oxazolidinones **28** to give *N*-alkynoyloxazolidinones **29** in moderate to good yields from the terminal alkyne **26** (Table 2).[10] Reductive coupling of these *N*-alkynoyloxazolidinones **29** with acid chlorides **15g−j** gave a series of divinyl (and aryl vinyl) ketones **30** in good to excellent yields (Table 2). Interestingly, the *N*-carboxyoxazolidinone-substituted dienones **30** were obtained as single double-bond isomers despite the extended conjugation through the dicarbonyl-substituted alkene. Presumably, the kinetically formed *Z*-isomer is also the thermodynamically most stable isomer.[11]

Nazarov substrates **30a−k** were configured in such a way as to allow for a systematic study of the effects of different substituents on the oxazolidinone ($R^1/R^{1'}$) and the dienone component (R^2 and R^3) upon Nazarov cyclization to give **31a−k**, respectively (Table 3). In the course of these studies, a number of stereoisomers **31A−D** were observed and accorded the following nomenclature *S*/*R*(oxazolidinone)-α,β(C4)-*cis*/*trans*(C4,5). The C4,5 *cis*,*trans*-stereochemistry of the cyclopentenone products was readily assigned on the basis of the coupling constant between H^4 and H^5, where *trans*-isomers **31A** and **31C** have a much smaller coupling constant, $J^{4,5}$ = 0.0−3.0 Hz ($J^{4,5}$ = 4.0−5.5 Hz for indanones) than that of the *cis*-isomers **31B** and **31D**, $J^{4,5}$ = 7.0−8.5 Hz.[12] The stereochemical assignment of C4-α

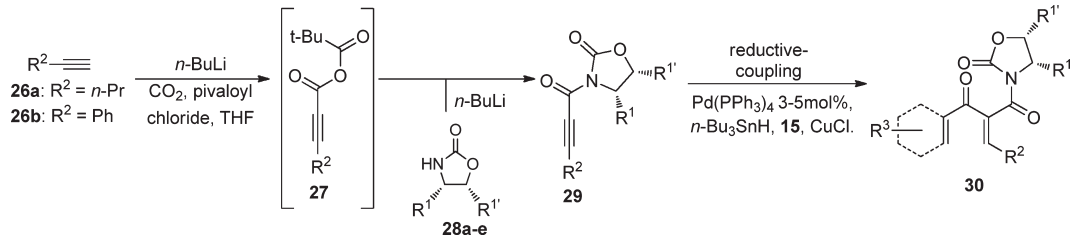
(8) In addition, $MeSO_3H$, $Cu(OTf)_2$, triflic acid, and $TiCl_4$ were also used, and all reactions were run CH_2Cl_2 at room temperature and at 60 °C (sealed tube).

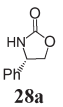
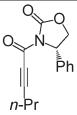
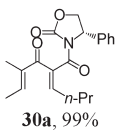
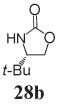
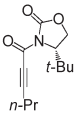
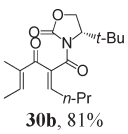
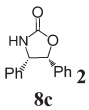
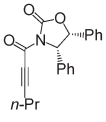
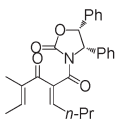
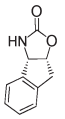
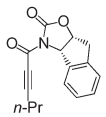
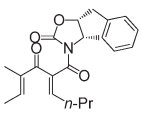
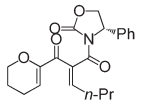
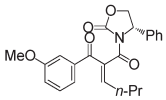
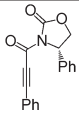
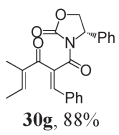
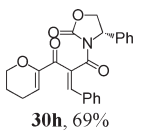
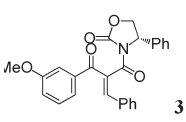
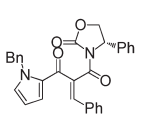
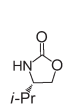
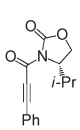
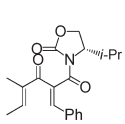
(9) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168. Smith, D. A.; Ulmer, C. W., II. *Tetrahedron Lett.* **1991**, *32*, 725. Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379.

(10) Fonquerna, S.; Moyano, A.; Pericas, Ma.; Riera, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1685.

(11) This stereochemical assignment is supported by the NOESY spectra of **30g** (see the Supporting Information) and is similar to that seen in related structures: Tietze, L. F.; Schuenke, C. *Eur. J. Org. Chem.* **1998**, 2089.

TABLE 2. Oxazolidinone Bearing Nazarov Precursors 30



Entry	26	28	29, yield%	15	30, yield%
1				**15g**	
	26a	**28a**	**29a**, 65%		**30a**, 99%
2	**26a**			**15g**	
		28b	**29b**, 43%		**30b**, 81%
3	**26a**			**15g**	
		28c	**29c**, 42%		**30c**, 86%
4	**26a**			**15g**	
		28d	**29d**, 43%		**30d**, 86%
5			**29a**	**15j**	
					30e, 70%
6			**29a**	**15k**	
					30f, 91%
7				**15g**	
	26b	**28a**	**29e**, 41%		**30g**, 88%
8			**29e**	**15j**	
					30h, 69%
9			**29e**	**15k**	
					30i, 79%
10			**29e**	**15i**	
					30j, 72%
11	**26b**			**15g**	
		28e	**29f**, 48%		**30k**, 92%

and C4-β for each of the *trans*-isomers **31a**−**kA** and **31a**−**kC** was made on the basis of comparable ^{1}H and ^{13}C NMR data between the compounds for which an X-ray crystal structure was obtained, **31aC** and **31hA**, and all the other *trans*-products.[3h,13] The C4-α/β stereochemistry of *cis*-isomers, **31B** and **31D**, was assigned on the basis of their partial isomerism to the corresponding *trans*-isomer upon standing (neat, usually 5−15 days at room temperature). *Exo*-isomers **31E** were not isolated but were observed in the ^{1}H NMR of the crude reaction mixtures by virtue of their characteristic *gem*-olefinic doublets (J^{gem} = 1.6−2.0 ppm) at 6.0−6.3 and 5.2−5.4 ppm.

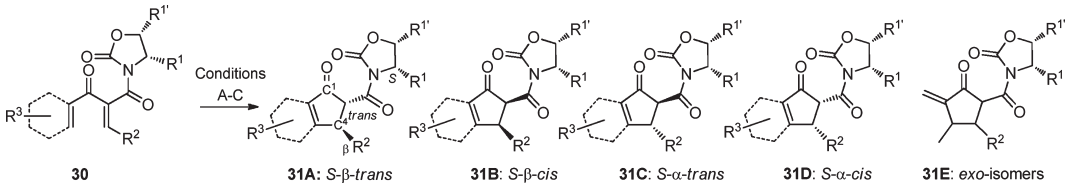
In order to identify the most effective reaction conditions for cyclizing the Nazarov precursors **30**, the simple alkyl-substituted divinyl ketone **30a**, bearing an *S*-phenyloxazolidinone auxiliary, was treated with several different Lewis acids ($Cu(OTf)_2$, $FeCl_3$, and $SnCl_4$) and $MeSO_3H$ in dichloromethane at different acid concentrations.[14] The best result was achieved using $MeSO_3H$ (10 equiv) in dichloromethane at −78 °C and then warming to room temperature for 12 h (Conditions A). This afforded **31a** as a mixture of isomers **31aA** and **31aC** in a 1:2.8 ratio; no *cis*-products were observed (entry 1, Table 3). While complete conversion and a similar level and sense of induction was also seen with 1 equiv\ of $MeSO_3H$ (not shown), considerable amounts of *exo*-double-bond isomers **31aE** were obtained; these result from proton

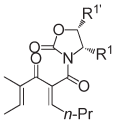
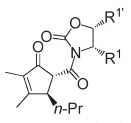
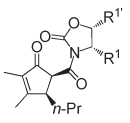
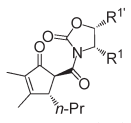
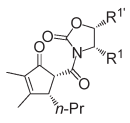
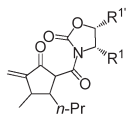
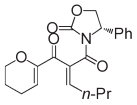
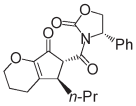
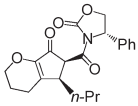
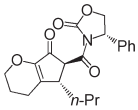
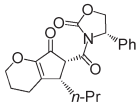
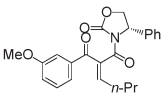
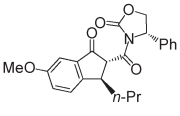
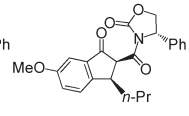
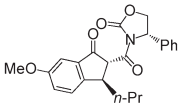
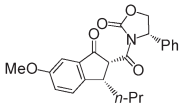
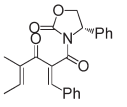
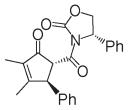
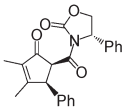
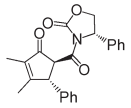
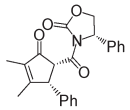
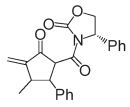
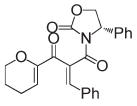
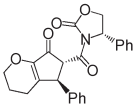
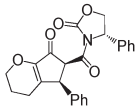
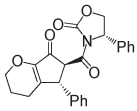
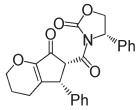
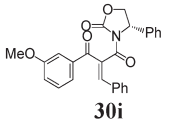
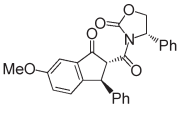
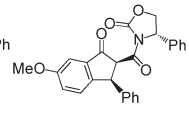
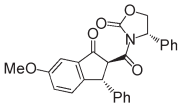
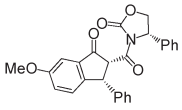
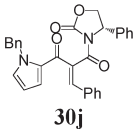
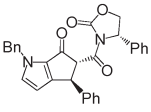
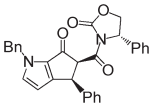
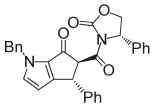
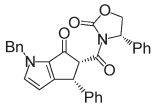
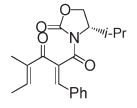
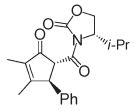
(12) Cocu, F. G.; Wolczunowicz, G.; Bors, L.; Posternak, T. *Helv. Chim. Acta* **1970**, *53*, 739.

(13) See Tables 5−7 in the Supporting Information. Most notably, the coupling constant of the two *trans* hydrogens in the oxazolidinone was consistently larger for all C4-β *trans*-isomers. See the Supporting Information for X-ray crystal structures of **31aC** and **31hA**.

(14) For a more complete listing of reaction conditions and product distributions, see Table 8 in the Supporting Information.

TABLE 3. Nazarov Cyclizations of 30 to 31



Entry	Substrate	Conditions[a]	Product, % amount by ^{1}H NMR (isolated yield %)				
			31A	**31B**	**31C**	**31D**	**31E**
1	 **30a** R = Ph, R$^{1'}$ = H	A	 **31aA**, 26 (24)	 **31aB**, 0	 **31aC**, 74 (71)	 **31aD**, 0	 **31aE**, 0
2	**30a** R = Ph, R$^{1'}$ = H	B	**31aA**, 31	**31aB**, 0	**31aC**, 48	**31aD**, 0	**31aE**, 21
3	**30b** R = *t*-Bu, R$^{1'}$ = H	A	**31bA** 22 (21)	**31bB**, 0	**31bC** 78 (74)	**31bD**, 0	**31bE**, 0
4	**30c** R = R$^{1'}$ = Ph	A	**31cA**, 28 (26)	**31cB**, 0	**31cC** 72 (71)	**31cD**, 0	**31cE**, 0
5	**30d** R, R$^{1'}$ = indanyl	A	**31dA**, 24 (23)	**31dA**, 0	**31dC**, 76 (70)	**31dD**, 0	**31dE**, 0
6	 **30e**	A	 **31eA**, 32 (27)	 **31eB**, 0	 **31eC**, 68 (65)	 **31eD**, 0	–
7	 **30f**	A[b]	 **31fA**, 28 (26)	 **31fB**, 0	 **31fC**, 46 (43)	 **31fD**, 0	–
8	 **30g**	A	 **31gA**, 31	 **31gB**, 41	 **31gC**, 17	 **31gD**, 11	 **31aE**, 0
9	**30g**	C	**31gA**, 0	**31gB**, 63 (70)	**31gC**, 0	**31gD**, 23	**31aE**, 13
10	**30g**	B	**31gA**, 60 (65)	**31gB**, 8	**31gC**, 16 (10)	**31gD**, 2	**31bE**, 14
11	 **30h**	B	 **31hA**, 70 (48)	 **31hB**, 9	 **31hC**, 13 (8)	 **31hD**, 8	–
12	**30h**	C	**31hA**, 7	**31hB**, 68 (64)	**31hC**, 2	**31hD**, 23	–
13	 **30i**	A	 **31iA**, 71 (68)	 **31iB**, 15	 **31iC**, 13 (5)	 **31iD**, 0	–
14	 **30j**	B[c]	 **31jA**, 56 (51)	 **31jB**, 18 (16)	 **31jC**, 22 (18)	 **31jD,** 4	–
15	**30j**	C	**31jA**, 0	**31jB**, 82 (81)	**31jC**, 0	**31jD,** 18 (10)	–
16	 **30k**	B	 **31kA**, 51 (50)	**31kB**, 6	**31kC**, 22 (23)	**31kD**, 5	**31kE**, 16

[a]Key: (A) $MeSO_3H$ (5−10 equiv), −78 °C to rt, 1−24 h, CH_2Cl_2, then $NaHCO_3$ (aq); (B) $Cu(OTf)_2$ (1.1 equiv), −78 °C to rt, 1−48 h, CH_2Cl_2, then $NaHCO_3$ (aq); (C) $MeSO_3H$ (10 equiv), −78 to 0 °C, 0.5−2 h, then $NaHCO_3$ (aq). [b]Starting material **30f** represented the majority of remaining product on the basis of ^{1}H NMR of the crude reaction mixture. [c]Reflux for 48 h.

elimination from the C2-methyl group in cyclopentenyl cation intermediate **3** (R^1 = Me). Presumably, the higher acid concentration used in Conditions A were effective in isomerizing the initially formed *exo*-isomers to the *endo*-isomers **31aA** and **31aC**. An X-ray crystal structure was obtained for the major product, confirming its assignment as the *S*-*β*-*trans* diastereomer **31aC**.[13] Since the ^{1}H NMR of the minor isomer indicated that it was also *trans*, it was assigned the *S*-*β*-*trans* stereochemistry **31aA**. Cyclization of **30a** to **31a** using $Cu(OTf)_2$ (1.1 equiv) in dichloromethane at −78 °C and then warming to room temperature for 12 h (Conditions B) gave a similar sense of diastereoselection but with a slightly reduced toquoselectivity (1:1.6) and a significant amount of *exo*-isomers **31aE** (entry 2, Table 3). Other Lewis acids, $FeCl_3$ and $SnCl_4$, gave some products **31aA** and **31aC** but produced significant quantities of byproduct (not shown).[14] Oxazolidinone auxiliaries bearing more bulky substituents than the phenyl group were also evaluated, **30b**−**d** (entries 3−5, Table 3). All cyclization reactions, **30b**−**d** to **31b**−**d**, were performed under Conditions A and produced ratios of **A** and **C** stereoisomers almost identical to those seen for **31a**. The stereochemical assignment of the **A** and **C** isomers for **31b**−**d** was based on a combination of the R_f's (TLC silica) and consistent patterns in the ^{13}C NMR when compared to **31aA** and **31aC**, though these assignments are only tentative.[13] Since there was no improvement in torquoselectivity using these other auxiliaries, the *S*-phenyloxazolidinone auxiliary was used in the subsequent reactions exploring substituent variations at C2−4 (entries 6−13, Table 3). Cyclization of the dihydropyran **30e** and methoxybenzene **30f** fused systems to **31e** and **31f**, respectively, gave a similar sense of torquoselectivity, favoring the **C** isomer, as seen in the corresponding dimethyl systems **30a**−**d** (entries 6 and 7, Table 3). However, the level of induction in the case of **31f** (**A**/**C** = 1:1.7) was somewhat lower than that observed in the other cases **31a**−**e**. The replacement of the C4-propyl group in **30a** for a phenyl group, as in **30g**, had a significant effect on the product distribution of the Nazarov reaction when performed under identical conditions, Conditions A (compare entries 1 and 8, Table 3). These conditions favored *cis*-product formation and a reversal in the torquoselectivity (**A** + **B**/**C** + **D**, 2.6:1) giving **31gB** as the major product. The yield of **31gB** was optimized when the reaction was performed using $MeSO_3H$ (10 equiv) at −78 °C and warming to 0 °C, rather than room temperature, prior to quenching with $NaHCO_3$ (Conditions C), giving the product in 70% isolated yield (entry 9, Table 3).[15] On the other hand, cyclization of **30g** with $Cu(OTf)_2$ (conditions B) favored the *trans*-product **31gA**, giving this product in a 65% isolated yield (entry 9, Table 3).[15] This reversal in the torquoselectivity in moving from a C4-alkyl to a C4-phenyl substituent was also seen with other Nazarov precursors **30h**−**k**. $Cu(OTf)_2$ (Conditions B) favored C4-*β* isomer **31hA**; unfortunately, chromatography of **31hA** proved problematic and a lower than anticipated isolated yield (48%) of this product was obtained (entry 11, Table 3). Compound **31hA** was crystallized and an X-ray crystal structure obtained.[13] The corresponding *cis*-product **31hB** was obtained in a 64% yield under Conditions C (entry 13, Table 3). Cyclization of **30i** to give indanone **31i** was only effectively achieved using $MeSO_3H$ (Conditions A) and strongly favored the *S*-*β*-*trans*-product **31iA** (entry 12, Table 3). The use of $Cu(OTf)_2$ (Conditions B) returned mostly starting material **30i** (not shown).[14] In the case of the pyrrolic Nazarov precursor **30j**, cyclization using Conditions B again favored the *trans*-*β*-isomer **31jA** (required heating) and Conditions C the *cis*-isomer **31jB** (entries 14 and 15, respectively, Table 3).

In order to ascertain as to whether the change in the nature of the product distribution in moving from C4-alkyl to C4-phenyl in **31** was specific to the phenyloxazolidinone, we also investigated the combination of an alkyl-substituted oxazolidinone (*S*-isopropyloxazolidinone) and a C4-phenyl group (entry 16, Table 3). Thus, cyclization of **30k** under Conditions B provided a similar product distribution of **31kA**−**D** as that seen for cyclization of **30g** to **31gA**−**D** under these conditions (compare entries 10 and 16, Table 3).

In light of the significance of the 4-isopropyl-6-oxo-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole unit as a substructure within the anticancer natural product (+)-roseophilin, we undertook the asymmetric synthesis of the benzyl protected system **37** (Scheme 3).[16] Initial *gem*-dibromo-olefination of isobutyraldehyde (**32**) to give **33**, followed by a Corey-Fuchs variant of our one-pot synthesis of *N*-alkynoyloxazolidinones using the lithiated *R*-phenyloxazolidinone **34**, gives **35** in good yield (69%). Reductive-coupling of **35** with the pyrroloyl chloride **15i** afforded Nazarov precursor **36** in an excellent yield (91%). Interestingly, in the Nazarov cyclization of **36** the torquoselectivity switched depending on whether a Brønsted acid (Conditions A) or a Lewis acid (Conditions D and E) was used (Table 4). Of the acids used, $FeCl_3$ (Conditions E) proved the most effective, giving a 3.5:1 ratio for the two *C4*-α/*β*-epimers and diastereomer **37A** in 75% yield (entry 3, Table 4). Presumably, some isomerism of **37B** to **37A** occurred during chromatography, affording **37A** in a higher yield than that indicated by the ^{1}H NMR of the crude reaction mixture. The auxiliary in **37A** could be removed to afford the decarboxylated product ***R*-21** (99%), with reasonable recovery of the auxiliary **34** (71%) (eq 4). Chiral HPLC indicated the presence of a minor amount of the other enantiomer (96% ee). Since both acidic and basic (LiOH, THF/H_2O, not shown) hydrolysis of the same sample of **37A** gave an identical ee for the product ***R*-21** and sustained heating under the reaction conditions of acid hydrolysis did not further reduce the ee, epimerization under the reaction conditions was not considered responsible for the presence of a minor amount of the other enantiomer. Most likely, a combination of < 100% enantiomeric purity of the auxiliary (99% *R*-enantiomer based on vendor specifications) and the presence of trace amounts of some **37C** or its *cis*-isomer in the sample of **37A** used in the decarboxylation was responsible for the presence of the minor enantiomer. This synthesis ***R*-21** and the diastereoselective substitution of racemic **21** (Scheme 2), demonstrate the synthetic utility of this auxiliary mediated approach to highly substituted cyclopentanoids.

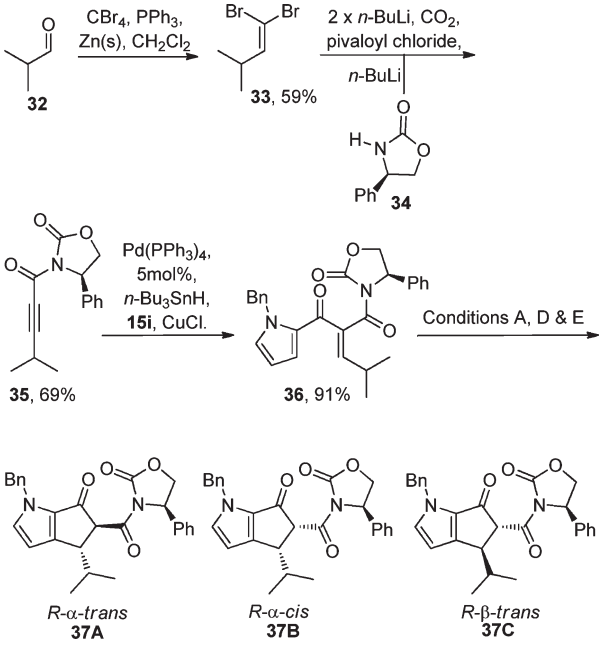
(4)

In order to explain the key observations made during the course of this study we have developed a tentative mechanistic

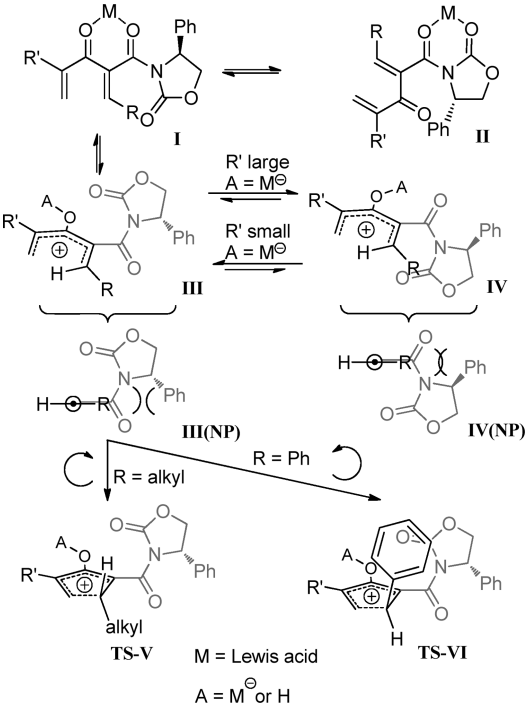
(15) The higher isolated yield of **31gB** under conditions C and **31gA** under conditions B than that indicated by ^{1}H NMR of the crude reaction mixture (entries 9 and 10, respectively, Table 3) is presumably due to the isomerism of the *exo*-isomers to *endo*-isomers upon workup and/or chromatography.

(16) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582.

SCHEME 3. Pyrrolo-Fused Cyclopentanones



SCHEME 4. Origins of Torquoselectivity



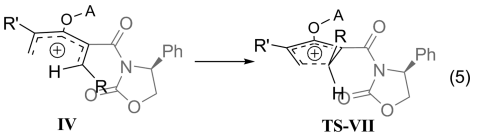
proposal for the role of the oxazolidinone auxiliary in determining the torquoselectivity of the Nazarov cyclization (Scheme 4). In this proposal, the method by which Lewis and protic acids interact with the substrate and induce torquoselectivity in the transition state of cyclization (**TS-V/VI**) are expected to be quite similar. This unified proposal of the role of protic and Lewis acids in the cyclization of substrates **30** has been devised to help explain the similar sense and level of induction seen with these different acids, including the switch in the sense of toquoselectivity in going from C4-alkyl to C4-Ph in **31**. While Lewis acids are expected to form chelates with the 1,3-dicarbonyl substrates, giving either **I** or **II**, we propose that, in order for a pentadienyl cation to form, **I** undergoes dechelation to give **III** or **IV**. This dechelation allows the carbonyl connected to the pentadienyl cation to rotate 90° out of plane with the pentadienyl cation, minimizing unfavorable electronic interactions between the electron-deficient π-system of the carbonyl and that of the delocalized π-cation. Also, in the complex **III**/**IV** (A = M^-), the anionic metal has a decreased requirement to complex to both carbonyls. In the case of protic acids, where chelation is not anticipated, pentadienyl cations **III**/**IV** (A = H) are expected to result directly from protonation of substrates **30**. In order to minimize dipole−dipole interactions, the two carbonyls in **III**/**IV** are expected to adopt an antiperiplanar conformation as they do in the products (see crystal structures, Figures A and B in the Supporting Information). Consequently, preference for either conformer **III** and **IV** will depend on the relative levels of steric interaction between the Ph group on the oxazolidinone (PhOx) and the two diastereotopic groups on the pentadienyl cation, R and OA. In most cases, **III** is expected to be preferred due to reduced steric interations between R and PhOx [see Newman projections **III**(**NP**) and **IV**(**NP**)], particularly where A = H or where A = M^- and R′ is relatively small, allowing A to occupy the site that is *transoid* to the oxazolidinone, as shown in **III**. Where R′ is large and A = M^-, A is expected to be buttressed into the *cisoid* position relative to the oxazolidinone, increasing the steric effects of OA (OM^-) with PhOx, favoring conformer **IV**. In most cases for **30**, R′ is small and conformer **III** is favored. As conformer **III** approaches the transition state of the reaction, **TS-V/TS-VI**, only the least obstructed face of the oxazolidinone is orientated toward the group R. Nonetheless, this is still larger than the oxygen atom that sits below the plane of the pentadienyl cation and where R = alkyl it is expected that the larger oxazolidinone ring will sterically repel R leading to a clockwise rotation, as in transition state **TS-V**. This model of induction may explain why the same level of modest diastereoselection (1:2.8) is seen for all systems **31a**−**d**, despite the significant variation in the size of the oxazolidinone substituent(s). If all oxazolidinones give a high preference for **III** over **IV**, than the torquoselectivity will be based only on the size difference between the oxygen atom and the unsubstituted face of the oxazolidinone, which is the same in all cases. For R = aryl, it is proposed that a positive π-stacking interaction between this phenyl and the oxazolidinone carbamate results in an anticlockwise rotation in **TS-VI**, explaining the reversal in

TABLE 4. Conditions for Formation of 37A−C

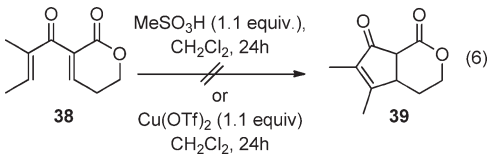
		Product, % by ^{1}H NMR (isolated yield %)		
Entry	Conditions	**37A**	**37B**	**37C**
1	A: $MeSO_3H$ (10 equiv), −78 °C to rt, 48 h	32	0	68
2	D: $Cu(OTf)_2$ (1 equiv), CH_2Cl, reflux, 24 h	70	0	30
3	E: $FeCl_3$ (1 equiv), CH_2Cl_2, reflux, 18 h	70 (75)	8 (0)	22 (21)

torquoselectivity for R = Ph versus R = alkyl. This is consistent with the fact that both a Ph (PhOx) and an *i*-Pr substituent on oxazolidinone induce the same sense of diastereoselection for R = Ph in the cyclization of **30g** and **30k** (entries 9 and 13, Table 3). Clearly, π-stacking between R = Ph and PhOx is not responsible for the switch in diastereoselection in going from R = alkyl to R = Ph. Similar π-stacking interactions between the C4-Ph substituent and the oxazolidinone carbamate may also explain the higher preference for *cis*-isomers in products **31** (R^2 = Ph) relative to **31** (R^2 = *n*-Pr) (Table 3). Notably, such a preference for *cis*-isomers was not seen for system **17** bearing a C4-Ph and a C5-carboxylate (Table 1).

This mechanistic proposal can be used to explain the observation that Lewis acids, $Cu(OTf)_2$ and $FeCl_3$, give the opposite torquoselectivity to the protic acid $MeSO_3H$ in the cyclization of the *N*-benzylpyrrolic substrate **36** to **37**. In this case, R′ = *N*-Bn in **III**/**IV**, and this relatively large group will tend to buttress Lewis acids (A = M^-) toward the oxazolidinone and sterically interfere with the PhOx group in **III** and favor **IV**. As conformer **IV** cyclizes the R group will rotate in an anticlockwise direction in the transition state **TS-VII** (eq 5), so as avoid interacting with the oxazolidinone (note, that the *R*-phenyloxazolidinone was used in **36**, not the *S*-enantiomer shown in **TS-VII**). However, for protic acids (A = H) the buttressing effect will be minimal and R in **III**/**IV** will be larger than OA (OH), favoring conformer **III** and transition state **TS-V**. This raises the question as to why **30j** gives the same sense of torquoselectivity irrespective of whether a Lewis or protic acid is used. We propose that under protic conditions (A = H), **III** will be favored and the Ph group attracted to the oxazolidinone due to π-stacking in the transition state **TS-VI**, as explained previously. However, when a Lewis acid is employed (A = M^-) conformer **IV** is favored over **III**, giving rise to **TS-VII** where the PhOx group disrupts π-stacking between R = Ph and the oxazolidinone carbamate and sterically repels this group, favoring anticlockwise rotation in **TS-VII**. Thus, where R = Ph and R′ is large, the same torquoselectivity is expected irrespective of whether a Lewis or Brønsted acid is used, albeit for different reasons.



The above proposal is based on an expectation that the carbonyl linking the oxazolidinone to the pentadienyl cation in **III** will be oriented perpendicular to the plane of the pentadienyl cation (Scheme 4). This is at odds with the previous proposal of a "polarized" Nazarov, where a combination of an electron-donating (EDG) and an electron-withdrawing group (EWG), **1** (R^1 = EDG, R^3 = EWG), promotes the Nazarov reaction in a donor−acceptor mode in the transition state of cyclization.[2c,17] Such a donor−acceptor arrangement would require an in-plane carbonyl to establish overlap with the pentadienyl cation in order to receive electron density from the π-donor. A major component of the evidence given in support of a "polarized" Nazarov has been based on the observation that cyclization reactions involving α-carboxyl systems **1** (R^3 = carbonyl) cyclize faster than the equivalent systems **1** (R^3 = H). However, as explained above for **16l**, this change in reaction rate can also be attributed to conformational changes, which slow down the cyclization of **1** (R^3 = H). A further point of evidence in support of our proposal, that a carbonyl will tend to deconjugate from pentadienyl cation in Nazarov reactions, comes from the observation that the conformationally restricted divinyl ketone **38** resists cyclization to **39** (eq 6).[18] Under conditions identical to that which readily cyclized the closely related acyclic esters **16m** and **16n** (Table 1 entries 11 and 14, respectively), compound **38** remained unchanged. This resistance to Nazarov cyclization can be explained using the mechanistic model introduced here, where the inability of the lactone carbonyl in **38** to rotate out of the plane of the pentadienyl cation raises its energy of formation and impedes cyclization.



As mentioned previously, the very similar patterns of diastereoselection observed for both protic and Lewis acids in the Nazarov cyclizations of **30** to **31**, have prompted us to propose a unified mechanism for both acid classes. Thus, we have proposed a monodentate transition state for the Lewis acid mediated cyclization of Nazarov substrates bearing α-carbonyl groups **1** (R^3 = carbonyl). However, a bidentate transition state cannot be ruled out and others have tentatively proposed these in order to explain the torquoselectivity they have observed in chiral Lewis acid mediated Nazarov cyclizations of similar substrates **1** (R^3 = carbonyl).[2g] Further studies will be required to verify the status of these reaction mechanisms.

Conclusion

In conclusion, the combination of reductive-coupling and Nazarov cyclization constitutes a formal (3 + 2)-cycloaddition of α,β-unsaturated acid chlorides with alkynoyl substrates to give flexible, functional group tolerant access to cyclopentenones and indanones. The carboxyl substituent in the alkynoyl substrate promotes the reductive-coupling and controls the regioselective placement of the substituent in the product (proximal to the carbonyl). This carbonyl also controls the regiochemical placement of the double bond in the cyclopentenone product of Nazarov cyclization (distal to the carbonyl) and can be used as a labile linker to a chiral oxazolidinone auxiliary for asymmetric Nazarov reactions. While the torquoselectivity of these reactions is only modest (~3:1), the high yields obtained in most cases and the capacity to separate diastereomers by chromatographic separation prior to facile auxiliary cleavage, make this an attractive, practical method for preparing chiral cyclopentanoids. Furthermore, it is anticipated that the results gained in this work and the associated mechanistic considerations will aid future auxiliary and catalyst design.

(17) (a) He, W.; Xiufeng, S.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278. (b) He, W.; Herrick, I. R.; Atein, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.

(18) Chaplin, J. H.; Kerr, D. J.; Flynn, B. L. Unpublished results.

Experimental Section

General Procedure A: Reductive Coupling 14 + 15 → 16 and 29 + 15 → 30. $Pd(PPh_3)_4$ (0.03 mmol) was added to a solution of THF (7 mL) or generated in situ by addition $Pd(dba)_2$ (3 mol %) to a solution of PPh_3 (0.12 mmol) followed by stirring for 0.5 h at 18 °C. To this solution was added alkyne **14** or **29** (1.0 mmol) followed by dropwise addition of Bu_3SnH (1.05 mmol), and then the reaction was allowed to stir for 10−30 min. Organic halide **15** (1.1 mmol) and CuCl (0.8 mmol) were then added, and the reaction was stirred at 18 °C for 5−30 h, monitoring consumption of intermediate alkenyl stananne by TLC (silica). KF(aq) (30%, 20 mL) was added and the reaction stirred for 2 h. The triphasic (organic, aqueous, and solid) mixture was filtered through Celite, washing with ethyl acetate (25 mL). The aqueous phase was separated from the organic phase and further extracted with ethyl acetate (25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (silica gel) giving the product **16** or **30**.

Typical Procedure for Nazarov Cyclization of Precursors 16 Using Methanesulfonic Acid. (±)-2-Hydroxymethylene-4,5,6-trimethoxy-3-phenylindan-1-one (17j). Methanesulfonic acid (61 μL, 0.92 mmol) was added to a solution of **16j** (50.0 mg, 0.153 mmol) in dry dichloromethane (2 mL). After being stirred for 30 min, the solution was diluted with diethyl ether (10 mL), washed with distilled water (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give **17n** as a slightly colored solid (49.4 mg, 99%): mp = 66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.80 (broad singlet, 1H), δ 7.10 − 7.20 (m, 7H), 4.89 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 196.0 (C), 161.5 (CH), 154.9 (C), 150.1 (C), 148.1 (C), 141.9 (C), 140.1 (C), 132.8 (C), 128.4 (CH), 127.6 (CH), 126.8 (CH), 120.1 (C), 100.6 (CH), 60.8 (CH_3), 59.9 (CH_3), 56.2 (CH_3), 44.3 (CH); IR (KBr disk, cm^{-1}) 3420, 3058, 3026, 2934, 2853, 1693, 1675, 1595, 1527, 1470, 1422, 1339, 1277, 1207, 1168, 1114, 1077, 1031, 951, 804, 697; LRMS (70 eV) *m*/*z* 326 ($M^{+\bullet}$, 95), 297 (100), 283 (30), 267 (25); HRMS calcd for $C_{19}H_{18}O_5$ 326.1154, found 326.1152.

Typical Procedure for Nazarov Cyclization of Precursors 16 using Cupric Triflate. (±)-*trans*-Methyl-5-(3-methoxyphenoxymethyl)-3,4-dimethyl-2-oxo-3-cyclopentenoate (17n). Cupric triflate (149 mg, 0.41 mmol) was added to a solution of **16n** (125 mg, 0.41 mmol) in dichloromethane (4 mL) and the solution stirred at 18 °C for 2 h. After this time, $NaHCO_3$ (5% w/v in H_2O, 10 mL) was added and stirring continued for a further 1 h. The biphasic mixture was separated and the aqueous layer extracted with dichloromethane (10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated onto silica gel (1 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, 5:5:2 hexanes/dichloromethane/diethyl ether) giving the product **17n** as a slightly tan oil (63.5 mg, 51%) and (*E*,*E*)-**16n** (16 mg, 11%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.1 Hz, 1H), 6.52 (dd, *J* = 8.1 Hz, *J* = 2.1, 1H), 6.45 (dd, *J* = 8.1 Hz, *J* = 2.1, 1H), 6.40 (t, *J* = 2.1 Hz, 1H), 4.14 (m, 2H), 3.78 (s, 6H), 3.50 (br s, 2H), 2.10 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 200.7 (C), 169.5 (C), 168.7 (C), 160.8 (C), 159.6 (C), 136.6 (C), 129.9 (CH), 107.0 (CH), 106.5 (CH), 101.1 (CH), 66.5 (CH_2), 55.3 (CH_3), 54.5 (CH), 52.7 (CH_3), 47.0 (CH), 15.1 (CH_3), 8.5 (CH_3); IR (KBr film, cm^{-1}) 2952, 1737, 1705, 1649, 1602, 1493, 1436, 1264, 1199, 1153; LRMS (70 eV) *m*/*z* 304 (M^+, 45), 273 (M^+ − MeO, 22), 181 (50), 149 (75), 137 (44), 124 (100); HRMS calcd for $C_{17}H_{20}O_5$ 304.1311; found 304.1315.

One-Pot Reductive-Coupling plus Nazarov-Cyclization Procedure. (±)-*trans*-*N*,*N*-Dimethyl-7-oxo-5-phenyl-2,3,4,5,6,7-hexahydrocyclopenta[*b*]pyran-6-carboxamide (17p). Tributyltin hydride (280 μL, 1.0 mmol) was added dropwise to a stirred solution of alkyne **14h** (173 mg, 1.00 mmol) and $Pd(PPh_4)_3$ (35 mg, 0.030 mmol) in dichloromethane (7 mL); this solution was then stirred for 30 min. After this time, acid chloride **15j** (161 mg, 1.10 mmol) and copper(I) thiophenecarboxylate (19 mg, 0.10 mmol) were added, and the reaction was stirred for 4 h. After this time, $MeSO_3H$ (133 μL, 2.0 mmol) was added and the reaction stirred for a further 1 h. The solvent was then removed under reduced pressure, the residue was dissolved in ethyl acetate (20 mL), saturated aqueous $NaHCO_3$ (20 mL) was added, and the resultant mixture was stirred for 1 h. The liquid phases were separated, and the organic phase was washed with aqueous KF (20%, 20 mL), the combined aqueous phases were re-extracted with ethyl acetate (20 mL), which was then washed with further KF (10 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and flash chromatographed (silica gel, 3:7 hexanes/ethyl acetate) giving the title compound **17p** as a crystalline solid (209 mg, 73%): mp = 157−160 °C; ^{1}H NMR (300 MHz, CDC_3) δ 7.38−7.24 (m, 3H), 7.17 (dd, *J* = 8.1, 1.2 Hz, 2H), 4.47 (d, *J* = 1.5 Hz, 1H), 4.21−4.08 (m, 2H), 3.63 (d, *J* = 1.5 Hz, 1H), 3.10 (s, 3H), 2.99 (s, 3H), 2.25 (m_c, 1H), 2.09 (m_c, 1H), 2.05−1.82 (m, 2H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 195.2 (C), 167.4 (C), 149.7 (C), 148.3 (C), 140.8 (C), 129.1 (CH), 127.6 (CH), 127.5 (CH), 67.0 (CH_2), 57.3 (CH), 47.8 (CH), 38.1 (CH_3), 36.2 (CH_3), 22.3 (CH_2), 21.4 (CH_2); LRMS *m*/*z* 308.3 (10, M + Na^+), 286.2 (100, MH^+); HRMS calcd for $C_{17}H_{19}NNaO_3^+$ 308.1263, found 308.1261; IR (cm^{-1}) 2933, 1718, 1628, 1492, 1400, 1124, 709.

(±)-1-Benzyl-4-isopropyl-4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one [(±)-21]. Sulfuric acid (880 μL, 16.2 mmol) was added dropwise to a stirred mixture of ester **17o** (878 mg, 2.70 mmol) and distilled water (1.5 mL) in ethanol (95%, 10 mL); this solution was then refluxed for 7 h. After this time, the reaction was cooled to room temperature and quenched with aqueous $NaHCO_3$ (5% w/v, 100 mL) before addition of dichloromethane (50 mL) and separation of the organic phase. The aqueous phase was re-extracted with dichloromethane (2 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated onto silica (3 g). Flash chromatography (silica gel, 85:15 hexane/ethyl acetate) gave the title compound (±)-**21** as a white solid (683 mg, 93%): mp = 37−38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 5.35−5.20 (m, 2H), 3.02−2.87 (m, 2H), 2.57 (dd, *J* = 16.8, 1.2 Hz, 1H), 1.83 (octet, *J* = 6.5 Hz, 1H), 0.95 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 191.1 (C), 154.6 (C), 137.3 (C), 134.0 (C), 133.4 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 106.2 (CH), 50.7 (CH_2), 46.4 (CH_2), 40.3 (CH), 32.2 (CH), 20.2 (CH_3), 19.6 (CH_3); LRMS *m*/*z* 507.5 (35, 2 × M + H^+), 254.2 (100, MH^+); HRMS calcd for $C_{17}H_{20}NO^+$ 254.1545, found 254.1547; IR (cm^{-1}) 3086, 2959, 2874, 1676, 1403, 1356, 1258, 1021, 729.

(±)-*trans*-1-Benzyl-4-isopropyl-5-(pent-4-enyl)-4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one (25). Lithium diisopropylamide (0.5 M in THF/cyclohexane, 0.66 mL, 0.33 mmol) was added slowly to a stirred solution of **23** (60.0 mg, 0.237 mmol) in THF (2 mL) at −78 °C, and the solution was then allowed to warm to room temperature. This solution was then recooled to −78 °C, and 5-iodopentene (70 mg, 0.36 mmol) was added. The solution was then allowed to come to room temperature and was stirred for 4 h. After this time, the reaction was taken up in diethyl ether (20 mL) and distilled water (40 mL). The organic phase was separated, and the aqueous phase was re-extracted with diethyl ether (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated onto silica (1 g). Flash chromatography (silica gel, 91:9 hexane/diethyl ether) gave the title compound **25** as a viscous oil (72.0 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.05 (d, *J* = 2.4 Hz, 1H), 5.80 (m_c, 1H), 5.27 (s, 2H), 5.03−4.92 (m, 2H), 2.69 (dd, *J* = 5.1, 1.4 Hz, 1H), 2.56 (ddd *J* = 6.9, 5.4, 1.4 Hz, 1H), 2.08 (q, *J* = 7.0 Hz, 2H), 1.92−1.42 (m, 5H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 193.8 (C), 153.0 (C), 138.7 (CH), 137.5 (C), 133.8 (CH), 133.7 (C), 128.8 (CH), 127.9 (CH), 127.7 (CH), 114.6 (CH_2), 106.4 (CH), 57.2 (CH), 50.8

(CH_2), 47.0 (CH), 34.1 (CH_2), 32.1 (CH_2), 32.0 (CH), 26.3 (CH_2), 21.1 (CH_3), 19.1 (CH_3); LRMS *m*/*z* 660.6 (10, 2 × M + NH_4^+), 643.6 (35, 2 × M + H^+), 322.2 (100, MH^+); HRMS calcd for $C_{22}H_{28}NO^+$ 322.2171, found 322.2170; IR (cm^{-1}) 3067, 2928, 1673, 1509, 1412, 910, 722.

General Procedure B: Preparation of *N*-Alkynoyloxazolidinones (29). *n*-Butyllithium (1.82 M in cyclohexane, 5.5 mL, 10.0 mmol) was added dropwise to a stirred solution of alkyne **26** (12.0 mmol) in THF (30 mL) at −78 °C under nitrogen. After the solution was stirred for 30 min, the nitrogen was turned off and CO_2(g) was bubbled slowly through the solution while it was warmed to 0 °C (ice bath) over the course of 30 min. The CO_2(g) supply was then removed and replaced with a N_2(g) atmosphere. The solution was again cooled to −78 °C, pivaloyl chloride (1.24 mL, 10.0 mmol) added, and the reaction mixture allowed to warm to room temperature for 3 h. The solution was then cooled again to −78 °C, and to it was added via cannula a solution of lithiated oxazolidinone (10.0 mmol, generated by addition of 5.5 mL of 1.82 M *n*-butyllithium solution to 10 mmol of oxazolidinone **28** in 60 mL of THF) at −78 °C. The solution was then allowed to warm to room temperature and stirred for 2 h. After this time, the solution was concentrated to a volume of 20 mL under reduced pressure. Ethyl acetate (50 mL) and distilled water (50 mL) were then added, the organic phase was separated, the aqueous phase was re-extracted with ethyl acetate (30 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated onto silica gel (5 g) under reduced pressure. The solid residue was subjected to flash chromatography to give purified **29**.

(*S*)-3-[(1*S*,5*S*)-3,4-Dimethyl-2-oxo-5-propylcyclopent-3-enecarbonyl]-4-phenyloxazolidin-2-one (31aC). Conditions A: Methanesulfonic acid (370 μL, 5.55 mmol) was added dropwise to a stirred solution of **30a** (190 mg, 0.555 mmol) in dichloromethane (4 mL) at −78 °C. This solution was allowed to warm to room temperature over a period of 2 h and then allowed to stir for a further 12 h. After this time, the acid was quenched by gradual addition of aqueous $NaHCO_3$ (5% w/v, 10 mL). After being stirred for 1 h, the mixture was taken up in extra dichloromethane (15 mL) and water (20 mL), the organic phase was separated, and the aqueous phase was then re-extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated onto silica gel (1 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, 50:50:7 hexane/dichloromethane/diethyl ether) giving the title compound **31aC**: white solid (134 mg, 71%); mp = 167−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.25 (m, 5H), 5.43 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.89 (d, *J* = 3.0 Hz, 1H), 4.76 (t, *J* = 8.6 Hz, 1H), 4.31 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.12 (m_c, 1H), 2.00 (s, 3H), 1.75 (m_c, 1H), 1.68 (s, 3H), 1.37−1.11 (m, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 201.1 (C), 173.2 (C), 168.8 (C), 153.7 (C), 139.2 (C), 133.9 (C), 129.0 (CH), 128.5 (CH), 125.6 (CH), 69.8 (CH_2), 58.1 (CH), 56.0 (CH), 46.5 (CH), 33.8 (CH_2), 20.4 (CH_2), 15.0 (CH_3), 13.8 (CH_3), 8.1 (CH_3); LRMS *m*/*z* 700.4 (20, 2 × M + NH_4^+), 359.4 (10, M + NH_4^+), 342.2 (100, MH^+); HRMS calcd for $C_{20}H_{24}NO_4^+$ 342.1705, found 342.1699; IR (cm^{-1}) 2925, 1778, 1716, 1691, 1489, 1197, 1023, 699. Minor isomer **31aA**: tan solid (45 mg, 24%); mp = 76−78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.23 (m, 5H), 5.46 (dd, *J* = 9.0, 5.9 Hz, 1H), 4.92 (br s, 1H), 4.71 (t, *J* = 8.9 Hz, 1H), 4.21 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.22 (m_c, 1H), 1.97 (s, 3H), 1.77 (m_c, 1H), 1.63 (s, 3H), 1.36−1.20 (m, 3H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 199.9 (C), 172.6 (C), 168.4 (C), 153.7 (C), 138.1 (C), 133.7 (C), 129.0 (CH), 128.4 (CH), 125.9 (CH), 69.7 (CH_2), 58.4 (CH), 56.6 (CH), 45.5 (CH), 34.0 (CH_2), 20.6 (CH_2), 15.0 (CH_3), 14.0 (CH_3), 8.2 (CH_3); LRMS *m*/*z* 700.5 (20, 2 × M + NH_4^+), 359.3 (10, M + NH_4^+), 342.2 (100, MH^+); HRMS calcd for $C_{20}H_{24}NO_4^+$ 342.1705, found 342.1718; IR (cm^{-1}) 2928, 1779, 1688, 1649, 1354, 1320, 1206, 755, 700.

(*S*)-3-[(1*R*,5*S*)-3,4-Dimethyl-2-oxo-5-phenylcyclopent-3-enecarbonyl]-4-phenyloxazolidin-2-one (31gA). Conditions B: Cupric triflate (75.0 mg, 0.207 mmol) was added to a stirred solution of **30g** (73.9 mg, 0.197 mmol) in dichloromethane (2 mL) at −78 °C. The reaction was stirred for 1 h at this temperature before being allowed to warm to room temperature where it was stirred for 18 h. After this time, the acid was quenched by addition of aqueous $NaHCO_3$ (5% w/v, 10 mL). After being stirred for 1 h, the mixture was taken up in extra dichloromethane (20 mL) and water (20 mL), the organic phase was separated, and the aqueous phase was re-extracted with dichloromethane (10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated onto silica gel (2 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, 50:50:6 hexane/dichloromethane/diethyl ether) giving the title compound **31gA**: white solid (65%); mp = 158−159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 − 7.48 (m, 8H), 7.14 (d, *J* = 6.3 Hz, 2H), 5.41 (dd, *J* = 9.0 Hz, *J* = 5.7 Hz, 1H), 5.21 (d, *J* = 2.1 Hz, 1H, H_a), 4.65 (t, *J* = 9.0 Hz, 1H), 4.42 (d, *J* = 2.1, 1H, H_b), 4.21 (dd, *J* = 9.0 Hz, *J* = 5.7 Hz, 1H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.7 (C), 170.8 (C), 167.4 (C), 153.4 (C), 140.0 (C), 138.2 (C), 134.3 (C), 129.1 (CH), 129.0 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 125.8 (CH), 69.7 (CH_2), 60.5 (CH), 58.3 (CH), 51.0 (CH), 15.3 (CH_3), 8.5 (CH_3); IR (KBr disk, cm^{-1}) 3048, 2927, 1782, 1700, 1637, 1393, 1332, 1282, 1221, 1120, 1063; LRMS (FAB) *m*/*z* 376 (MH^+ 100); HRMS (FAB) calcd for $C_{23}H_{22}NO_4$ (MH^+) 376.1549, found 376.1546. Minor isomer **31gC**: waxy solid (10%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.22 (m, 8H), 7.08 (dd, *J* = 7.8, 1.5 Hz, 2H), 5.41 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.18 (d, *J* = 3.0 Hz, 1H), 4.75 (t, *J* = 8.6 Hz, 1H), 4.30 (br s, 1H), 4.27 (dd, *J* = 8.7, 2.7 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 200.9 (C), 171.9 (C), 167.9 (C), 153.6 (C), 139.9 (C), 139.1 (C), 134.7 (C), 129.2 (CH), 129.0 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 125.8 (CH), 70.0 (CH_2), 59.9 (CH), 58.4 (CH), 52.0 (CH), 15.5 (CH_3), 8.5 (CH_3); LRMS *m*/*z* 768.5 (20, 2M + NH_4^+), 393.4 (10, M + NH_4^+), 376.3 (100, MH^+); HRMS calcd for $C_{23}H_{21}NNaO_4^+$ 398.1368, found 398.1368; IR (cm^{-1}) 2921, 1778, 1709, 1690, 1645, 1381, 1320, 1195, 701.

(*S*)-3-[(1*S*,5*S*)-3,4-Dimethyl-2-oxo-5-phenylcyclopent-3-enecarbonyl]-4-phenyloxazolidin-2-one (31gB). Conditions C: The reaction was performed as described for **31aC** using **30g** giving **31gB**, except that the reaction was warmed to 0 °C and stirred at this temperature for 0.5 h and then the aqueous $NaHCO_3$ (5% w/v) solution added. After flash chromatography (silica gel, ethyl acetate), the product **31gB** was obtained as a white solid (70%): mp = 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95−7.20 (m, 8H), 6.51 (d, *J* = 7.2 Hz, 2H), 5.22 (dd, *J* = 8.4 Hz, *J* = 3.3 Hz, 1H), 4.72 (d, *J* = 7.8 Hz, 1H), 4.57 (t, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 7.8 Hz, 1H), 4.10 (dd, *J* = 8.4 Hz, *J* = 3.3 Hz, 1H), 1.83 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.2, 171.1, 167.4, 153.5, 137.9, 137.5, 135.9, 129.3, 128.9, 128.5, 127.9, 127.8, 125.6, 70.3, 57.6, 56.5, 53.2, 15.7, 8.3; LRMS (70 eV) *m*/*z* 375 (M^+ 35), 212 (100); HRMS calcd for $C_{23}H_{21}NO_4$ 375.1471, found 375.1467.

(*R*)-3-[(4*S*,5*S*)-1-Benzyl-4-isopropyl-6-oxo-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-5-carbonyl]-4-phenyloxazolidin-2-one (37A). Conditions E: Ferric chloride (72 mg, 0.443 mmol) was added to a stirred solution of **36** (178 mg, 0.403 mmol) in dry dichloromethane (2.5 mL) at room temperature. This mixture was then refluxed for 18 h. After being cooled to room temperature, the reaction was quenched by gradual addition of aqueous $NaHCO_3$ (5% w/v, 20 mL). Extra dichloromethane (15 mL) was then added, and the organic phase was separated. The aqueous phase was then further extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated onto silica gel (2 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, sequential elution 4:1/3:1 hexane/ethyl acetate) giving the title compound **37A**: clear

solid (133 mg, 75%): mp = 64−66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.40 (m, 2H), 7.39−7.25 (m, 6H), 7.22−7.17 (m, 2H), 6.93 (d, J = 2.4 Hz, 1H), 6.07 (d, J = 2.4 Hz, 1H), 5.51 (dd, J = 9.2, 6.2 Hz, 1H), 5.48 (br s, 1H), 5.20 (s, 2H), 4.73 (t, J = 9.0 Hz, 1H), 4.24 (dd, J = 8.9, 6.2 Hz, 1H), 3.53 (dd, J = 6.8, 3.2 Hz, 1H), 1.94 (octet, J_{app} = 6.8 Hz, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 182.7 (C), 169.1 (C), 153.9 (C), 153.8 (C), 138.3 (C), 136.9 (C), 134.6 (CH), 131.6 (C), 129.0 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 126.0 (CH), 106.4 (CH), 69.7 (CH_2), 61.4 (CH), 58.5 (CH), 50.7 (CH_2), 43.7 (CH), 31.5 (CH), 20.3 (CH_3), 20.0 (CH_3); LRMS m/z 902.3 (20, 2 × M + NH_4^+), 460.3 (10, M + NH_4^+), 443.4 (100, MH^+); HRMS calcd for $C_{27}H_{27}N_2O_4^+$ 443.1971, found 443.1960; IR (cm^{-1}) 3032, 2959, 1776, 1676, 1354, 1198, 1062, 698. Minor isomer **37C**: thick gum (37 mg, 21%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.20 (m, 10H), 6.97 (d, J = 2.3 Hz, 1H), 6.09 (d, J = 2.3 Hz, 1H), 4.97 (d, J = 3.2 Hz, 1H), 5.46 (dd, J = 8.4, 2.7 Hz, 1H), 5.23 (s, 2H), 4.77 (t, J = 8.6 Hz, 1H), 4.30 (dd, J = 8.7, 2.7 Hz, 1H), 3.41 (dd, J = 6.8, 3.2 Hz, 1H), 1.94 (octet, J = 6.7 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (JMOD, 75 MHz, $CDCl_3$) δ 183.8 (C), 169.3 (C), 154.3 (C), 153.8 (C), 139.3 (C), 136.8 (C), 134.7 (CH), 131.8 (C), 129.1 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 125.6 (CH), 106.5 (CH), 69.8 (CH_2), 60.8 (CH), 58.1 (CH), 50.8 (CH_2), 44.7 (CH), 31.4 (CH), 20.1 (CH_3), 19.9 (CH_3); LRMS m/z 902.5 (35, 2 × M + NH_4^+), 443.4 (100, MH^+); HRMS calcd for $C_{27}H_{27}N_2O_4^+$ 443.1971, found 443.1974; IR (cm^{-1}) 3033, 2959, 1776, 1675, 1410, 1354, 1194, 1062, 761, 698.

(*R*)-1-Benzyl-4-isopropyl-4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one [(*R*)-21]. Sulfuric acid (203 μL, 3.70 mmol) was added dropwise to a stirred mixture of **37A** (273 mg, 0.617 mmol) and distilled water (0.35 mL) in ethanol (95%, 2.5 mL); this solution was refluxed for 7 h. After this time, the reaction was cooled to room temperature and quenched with aqueous $NaHCO_3$ (5% w/v, 25 mL) before addition of dichloromethane (15 mL) and separation of the organic phase. The aqueous phase was re-extracted with dichloromethane (2 × 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated onto silica (1.5 g). Flash chromatography (silica gel, sequential elution 85:15/1:1 dichloromethane/ethyl acetate) gave the title compound as a white solid (*R*)-**21** (154 mg, 99%) as well as recovered oxazolidinone **34** (71 mg, 71%): mp = 54−56 °C; $[\alpha]_D^{24}$ = −50.9 (c = 2.57, CH_2Cl_2, 96% ee); Chiral HPLC (150 × 4.6 mm, Phenomenex, Lux 5 μm Cellulose-1 column, 1 mL/min, 254 nm, 5% ethanol in hexane) t_1 = 5.70 min (minor), t_2 = 6.15 min (major). Spectra were identical to those of the racemate (±)-**21** (above).

Supporting Information Available: General experimental methods, NMR Tables 5−7, additional conditions used in the cyclization of compounds **30a**−**k** (Table 8), X-ray crystal data for **31aC** and **31hA**, detailed experimental procedures and spectral data for all additional compounds, copies of ^{1}H and ^{13}C NMR of all new compounds, copies of ^{1}H NMR of crude reaction mixtures listed in Table 8, and X-ray crystal structures of compounds **31aC** and **31hA** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.