JOC Article

Gold-Catalyzed Synthesis of Oxygen- and Nitrogen-Containing Heterocycles from Alkynyl Ethers: Application to the Total Synthesis of Andrachcinidine

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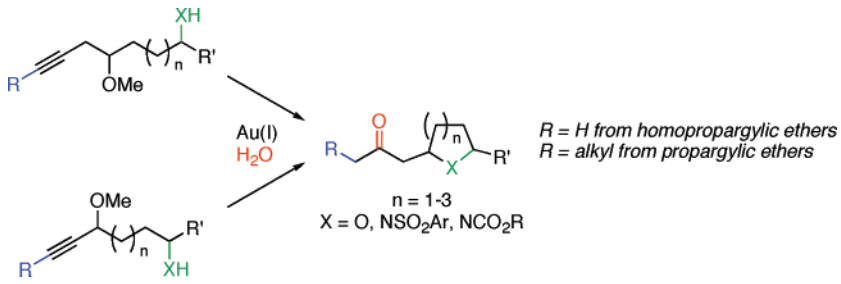

In this paper we report that homopropargylic ethers containing pendent oxygen or nitrogen nucleophiles react with electrophilic gold catalysts in the presence of water to form saturated heterocyclic ketones. Mechanistic studies demonstrated that the reactions proceed through a sequence of alkyne hydration, alkoxy group elimination, and intramolecular conjugate addition. Diastereoselectivities for tetrahydropyran and piperidine formation are very good to excellent. This method has been applied to an efficient total synthesis of the natural product andrachcinidine. Utilizing propargylic ether substrates rather than homopropargylic ethers promotes regioselective hydration of internal alkynes, thereby expanding the scope of products that can be accessed through this protocol.

Introduction

Saturated heterocycles are ubiquitous in natural products and pharmaceutical agents. For example, tetrahydrofuran subunits can be found in the annonaceous acetogenins,[1] tetrahydropyrans are present in several cytotoxins,[2] and larger oxygen-containing rings are components of the marine ladder toxins.[3] Substituted piperidine rings are common structural features in numerous alkaloids.[4] Additionally piperidine rings serve as attractive scaffoldings for medicinal agents because they can be converted to derivatives such as sulfonamides and carbamates that project functional groups into various spatial arrangements for binding to biological targets. Consequently new reactions in which saturated heterocycles can be prepared in a chemo- and stereoselective manner will be broadly applicable for endeavors in natural product synthesis and medicinal chemistry.

The synthesis of structurally complex heterocycles often requires selective manipulation of one functional group in the presence of other moieties with similar reactivity patterns. While this issue is commonly addressed through the judicious use of protecting groups, an attractive alternative approach exploits latent functional groups that can be revealed through highly chemoselective transformations. Alkene and alkyne activation by electrophilic transition metal catalysts is proving to be a successful strategy for achieving this objective, with gold reagents proving to be exceptionally effective and versatile.[5] Recent literature reports have shown that, in the presence of

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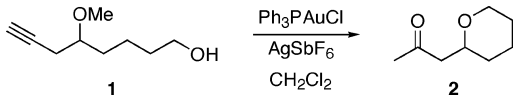
SCHEME 1. Gold-Mediated Tetrahydropyran Synthesis from a Homopropargylic Ether

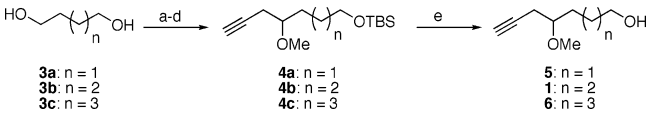


gold catalysts, alkynes can be converted to ketones,[6] vinyl esters,[7] acetals,[6,8] and heterocycles,[9] serve as electrophiles in carbon−carbon bond forming reactions,[10] and undergo a diverse range of sigmatropic[11] and skeletal rearrangements.[12] Alkenes have been transformed into ethers,[9a,13] esters,[13] and amine derivatives.[14] Following our observation that homopropargylic ether **1** can be converted to tetrahydropyran **2** (Scheme 1) in the presence of gold catalysts[15] we initiated a program directed toward optimizing this mild heterocycle synthesis, exploring its mechanism, and expanding its scope. In this paper we describe our use of homopropargylic ethers that, through gold catalysis, serve as latent α,β-unsaturated ketones and react with appended nucleophiles en route to saturated oxygen- and nitrogen-containing heterocycles. Mechanistic details of this multistep process will be presented, as will its application as the key step in the enantioselective total synthesis of the monocyclic alkaloid andrachcinidine.

Results and Discussion

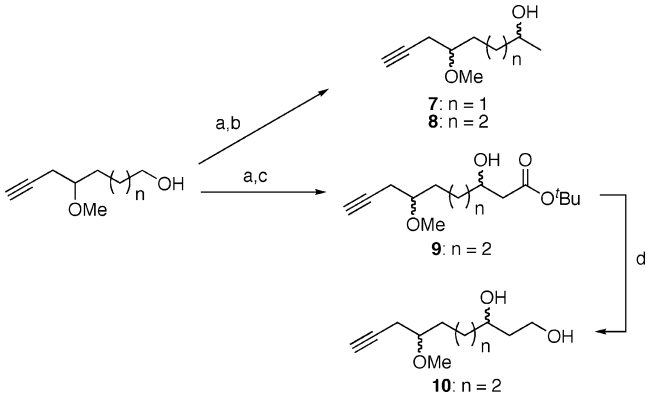
Oxacycle Substrate Synthesis. We prepared a range of substrates to study the mechanism and scope of the process. These substrates were designed to examine the facility of accessing multiple ring sizes, the capacity for diastereocontrol in the cyclization step, and the ability to conduct chemoselective cyclization reactions in the presence of other potentially reactive functional groups.

SCHEME 2. Synthesis of Primary Alcohol Substrates[a]



[a] Reagents and conditions: (a) NaH, THF, 0 °C, then TBSCl; (b) SO_3·pyridine, Et_3N, DMSO, CH_2Cl_2; (c) propargyl bromide, Zn, 1,2-diiodoethane, THF, sonication; (d) NaH, THF, 0 °C, then MeI; (e) HCl, H_2O, THF.

SCHEME 3. Preparation of Secondary Alcohol Substrates[a]



[a] Reagents and conditions: (a) PDC, CH_2Cl_2; (b) MeMgBr, THF, 0 °C; (c) LDA, *tert*-butyl acetate, THF, −78 °C; (d) $LiAlH_4$, Et_2O, −78 °C.

The synthesis of the initial group of substrates is shown in Scheme 2. Monosilylation[16] of α,ω-diols **3a**−**c** followed by oxidation,[17] Barbier-type propargyl addition,[18] and methylation provided silyl ethers **4a**−**c**. Desilylation yielded substrate **1** and its lower and higher homologues **5** and **6**.

Secondary alcohol substrates were readily prepared from the primary alcohols through straightforward sequences (Scheme 3). Oxidation followed by either Grignard reagent addition or aldol reaction with the lithium enolate of *tert*-butyl acetate provided substrates **7**−**9**. Reducing **9** with $LiAlH_4$ provided diol substrate **10**. No effort was made to control the stereochemical outcomes of these reactions at this point in the study.

Reaction Optimization. Initial efforts at converting **1** to **2** in the presence of various gold catalysts in CH_2Cl_2 under ambient conditions proved to be irreproducible. Noting the apparent requirement for water to effect the desired transformation, we employed CH_2Cl_2 that had been presaturated with water as the reaction solvent. Using this solvent and gentle heating (35 °C) with the cationic gold species that arises from mixing Ph_3PAuCl and $AgSbF_6$[10a,19] as the catalyst (procedure A) resulted in a reproducibly efficient conversion of **1** to **2**, with nearly quantitative yields of the volatile product being observed by gas chromatography. Neither Ph_3PAuCl nor $AgSbF_6$ alone promoted the transformation. The less expensive gold source $NaAuCl_4$ (procedure B) also promoted the process, albeit more slowly, providing good yields of the desired product. The highest

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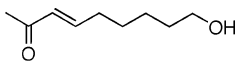

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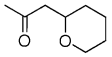
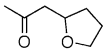
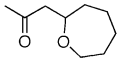
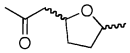
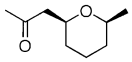
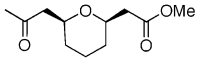
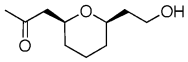
FIGURE 1. Enone byproduct from the cyclization of **6**.

TABLE 1. Scope of Oxacycle Forming Reactions

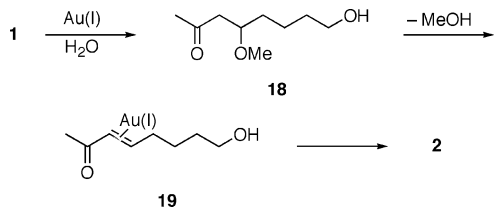
entry	substrate	product(s)	procedure[a]	time (h)	yield (%)[b]
1	**1**	 **2**	A	24	100[c]
			B	48	96[c]
2	**4b**	**2**	B	48	78%[c]
3	**5**	 **11**	B	12	85%[c]
4	**6**	 **12**	B	48	52%
5	**7**	 **14**	A	8	96%[c]
			B	8	92%[c] 55:45 dr
6	**8**	 **15**	B	48	74
7	**9**	 **16**	A	12	60%[d]
8	**10**	 **17**	A	48	97%
			B	48	70%

[a] Procedure A: Substrate in water-saturated CH_2Cl_2 (~60 mM), Ph_3PAuCl (5 mol %), $AgSbF_6$ (5 mol %), 35 °C. Procedure B: Substrate in water-saturated CH_2Cl_2 (~60 mM), $NaAuCl_4$ (5 mol %), 35 °C. [b] Yields are reported for isolated, purified products unless otherwise noted. [c] Yield determined by GC. [d] The *tert*-butyl ester was also isolated in 10% yield.

yields were observed when the catalyst was added in two portions, suggesting the possibility that the active catalytic species decomposed over time. Coordinating solvents such as THF or CH_3CN completely suppressed the reaction.

Cyclization Scope and Mechanism. To determine the scope of the reaction and to gain insight into its mechanism we subjected several substrates to procedures A and/or B. The results are shown in Table 1. Primary alcohol substrates cyclized smoothly to form tetrahydropyran and tetrahydrofuran structures (entries 1 and 3), and with moderate efficiency to form oxepane **12** (entry 4). An appreciable amount of enone **13** (Figure 1) was isolated in cyclization of **6**. Silyl ether **4b** also proved to be a suitable substrate for the process (entry 2), indicating that protected hydroxyl groups can serve as nucleophiles in the cyclization event. Secondary alcohols **8**−**10**, though prepared as diastereomeric mixtures, provided products as single stereoisomers (entries 6−8), while **7** provided a diastereomeric mixture of products (entry 5). Substrates that yielded tetrahydrofuran products showed faster starting material consumption than substrates that yielded tetrahydropyran products, and primary alcohols were generally consumed faster than secondary alcohols. Intermediates along the reaction pathway did not

SCHEME 4. Proposed Cyclization Mechanism



accumulate to a significant extent except when **6** was the substrate. The cyclization of ester **9** resulted in the isolation of the methyl ester as the major product, presumably due to alcoholysis of the *tert*-butyl ester by the MeOH that is released in the reaction, though the *tert*-butyl ester was also isolated as a minor product.

The formation of tetrahydropyrans **15**−**17** as single stereoisomers from diastereomeric mixtures of starting materials indicates that the stereogenic center that bears the methoxy group is lost or is subjected to stereochemical mutation during the course of the reaction. The possibility that the loss of stereogenicity is only relevant when secondary alcohols are used as nucleophiles was discounted by preparing **1** in enantiomerically enriched form through an asymmetric propargylation reaction[20] and subjecting it to the reaction conditions. Racemic product was isolated. The isolation of enone **13** from the cyclization of **6**, and the ability to convert it to the oxepane through resubjection to the reaction conditions, indicates that enone intermediates are formed during the transformation. These observations led us to propose the mechanistic pathway shown for the cyclization of **1** in Scheme 4, in which the initial step is ketone formation through alkyne hydration to yield **18**, followed by β-elimination of the methoxy group to form enone **19**, and gold-mediated conjugate addition of the nucleophilic hydroxyl group to provide **2**.

Several aspects of this mechanism merit further discussion. The initial alkyne hydration is well-precedented.[6] The elimination of the methoxy group has far less precedent. Utimoto and Fukuda observed[21] the gold-mediated conversion of *propargylic* ethers to enones, but that process is potentially mechanistically distinct as it proceeds through the formation of an enol intermediate that is adjacent to an alkoxy leaving group. The nucleophilic addition can simply be considered as the microscopic reverse of the elimination reaction. Several reports of gold-mediated additions of nucleophiles to alkenes have recently appeared in the literature,[9a,13,14] but these examples generally employ alkenes that are far more electron rich than the electron-deficient intermediates that appear in this work. Trost, however, has postulated[22] that ruthenium catalysts can promote tetrahydropyran formation through a similar mechanism and Kobayashi has reported[23] carbamates undergo conjugate additions with α,β-unsaturated carbonyl compounds in the presence of gold catalysts. In consideration of the mild reaction conditions and the apparent facility of the cyclization step (enones could not be isolated, or even observed by TLC, in reactions that provided tetrahydrofurans and tetrahydropyrans), these conditions should be generally useful for ring constructions that proceed through

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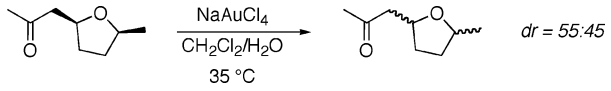
SCHEME 5. Product Equilibration under Cyclization Conditions

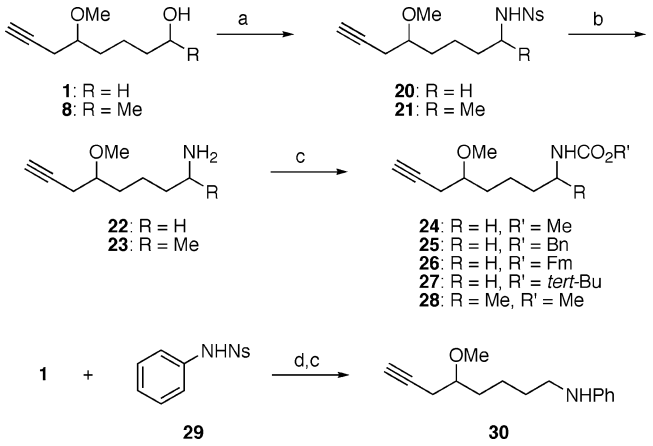


heteroatom addition into α,β-unsaturated carbonyl compounds.[24] Phosphine-catalyzed ring formation[25] can be discounted because of the ability of ligand-free $NaAuCl_4$ to promote the process. While Brønsted acid catalysis of the latter steps in the sequence[26] cannot be rigorously ruled out, exposing **1** to HCl in wet CH_2Cl_2 at 35 °C resulted in the recovery of starting material, confirming the essential role of gold in initiating the process. Neither Ph_3PAuCl nor $AgSbF_6$ alone promoted the cyclization from any of the proposed intermediates, though the combination promoted cyclizations of enone and β-methoxy ketone intermediates, indicating that Brønsted acid, should it be a relevant catalyst, requires both catalysts to be generated. As noted above, the rate of starting material consumption is related to the rate of cyclization, even though the rate of alkyne hydration would appear to be unaffected by downstream events. This suggests that the gold catalyst is sequestered by an intermediate during the course of the reaction and is liberated upon cyclization. Two important advantages of this method from the perspective of synthetic strategy are illustrated in this study. The ability to use potent nucleophiles such as Grignard reagents or enolates for substrate preparation highlights the utility of homopropargylic ethers as enone surrogates, and the high selectivity of gold catalysts for alkynes eliminates the need to protect remote hydroxyl groups.

The stereochemical outcomes of these reactions could arise from kinetic control or, because the products are β-alkoxy ethers of the type that undergo elimination, through thermodynamic control. To address whether stereochemical equilibration can occur during the course of the reaction, we subjected a single diastereomer of tetrahydrofuran **14** to the reaction conditions (Scheme 5). After several hours a 55:45 mixture of diastereomers was formed, which was identical with the results from the initial reaction. Thus stereochemical outcomes from these reactions can be predicted based on thermodynamic grounds, with heightened *A*-values for substituents at the 2- and 6-positions of tetrahydropyrans[27] accounting for the exceptional diastereocontrol that is observed in their formation.

Application to Piperidine Synthesis. Our successful results in the area of oxygen-containing heterocycle synthesis led us to examine the potential for using the method to prepare nitrogen-containing heterocycles. Nitrogen nucleophiles have been used with great success in gold-catalyzed processes,[14,28] with the vast majority of reactions utilizing sulfonamides or carbamates rather than aliphatic amines. Our objective was to test the capacity of aliphatic amines, anilines, sulfonamides, and carbamates to serve as nucleophiles in this process and to determine whether the identity of the substituent on the nitrogen would impact the diastereoselectivity of the cyclization.

SCHEME 6. Synthesis of Nitrogen-Containing Substrates[a]



[a] Reagents and conditions: (a) $NsNH_2$, Ph_2PPy, DTBAD, CH_2Cl_2; (b) PhSH, $NaHCO_3$, CH_3CN; (c) R′OC(O)Cl or R′OC(O)OC(O)OR′, $NaHCO_3$, THF, H_2O; (d) Ph_3P, DIAD, CH_2Cl_2.

The substrates for this process were prepared (Scheme 6) from the corresponding alcohol substrates through facile sequences. Sulfonamides **20** and **21** were accessed directly from alcohols **1** and **8** and *o*-nitrobenzene sulfonamide ($NsNH_2$) under modified Mitsunobu conditions[29] by using di-*tert*-butyl azodicarboxylate (DTBAD) and Ph_2PPy. Cleavage with basic thiophenol[30] provided amines **22** and **23** that were converted to carbamates **24**−**28** with the appropriate chloroformates. Aniline **30** was constructed through a Mitsunobu reaction between **1** and phenyl sulfonamide **29** followed by cleavage with basic thiophenol.

The conditions that were successful for cyclization reactions of the oxygen-containing substrates proved to be unsuitable for promoting complete conversion of **20** to piperidine **31**. After extensive studies we discovered that changing the solvent from CH_2Cl_2 to water-saturated toluene and using a 2:1 ratio of $AgSbF_6$ to Ph_3PAuCl (procedure C) resulted in complete conversions and reproducible reaction times. Notably, toluene can be used directly from the bottle with no loss of yield. The results of exposing the nitrogen-containing substrates to these conditions are shown in Table 2. Also shown (entry 7) is the result of exposing oxygen-containing substrate **8** to procedure C. The reaction was complete within 1 h rather than the 48 h that were required for the initial conditions (Table 1), highlighting the dramatic rate enhancement that results from conducting the reaction in toluene.

As shown in the table, sulfonamides and most carbamates react smoothly to form piperidines in good to excellent yield, though the *tert*-butyl carbamate **27** did not yield any cyclization product. This is most likely due to steric interactions in the cyclization transition state. Free amine **22** and aniline **30** also failed to react, indicating that nitrogen basicity must be modulated for successful cyclization. Tanaka has proposed[31] that amines react with gold catalysts to form complexes that should

(24) For examples of this approach to heterocycle formation, see: (a) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481. (b) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816. (c) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463.

(25) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

(26) (a) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141. (b) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (c) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsonomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

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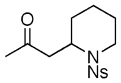
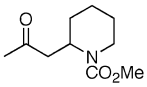
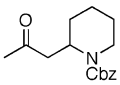
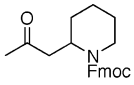
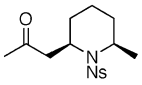
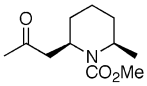
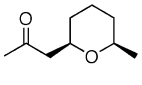
(28) For a review, see: Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.

(29) Guisado, C.; Waterhouse, J. E.; Price, W. S.; Jorgensen, M. R.; Miller, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1049.

(30) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

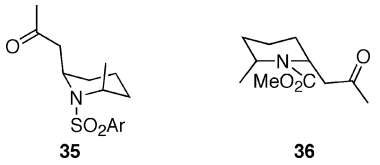
(31) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349.

TABLE 2. Gold-Mediated Piperidine Synthesis[a]

entry	substrate	product	time (h)	yield (%)[b]
1	**20**	 **31**	12	84
2	**24**	 **32**	48	91
3	**25**	 **33**	48	77
4	**26**	 **34**	48	84
5	**21**	 **35**	12	83 dr = 92:8
6	**28**	 **36**	48	84 dr = 87:13
7	**8**	 **15**	1	78
8	**22**	–[c]		
9	**27**	–[c]		
10	**30**	–[c]		

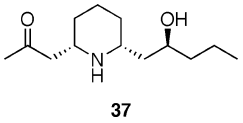
[a] Procedure C: Substrate in water-saturated toluene (~25 mM), Ph_3PAuCl (5 mol %), $AgSbF_6$ (10 mol %), 40 °C. [b] Yields are reported for isolated, purified products unless otherwise noted. [c] Starting material was largely unconsumed in these reactions.

be substantially less electrophilic than cationic Au(I) catalysts, and Krause reported[32] that utilizing aliphatic amines in gold-catalyzed cyclization reactions results in substantially diminished rates when compared to the corresponding sulfonamides (5 d vs 1 h), though rates can be improved with appropriate catalyst selection.[33] As observed in the oxacycle syntheses, $AgSbF_6$ alone does not promote any of the steps in the sequence, suggesting that excess silver in these reactions simply promotes more efficient generation of the relevant cationic Au(I) catalyst. Branched sulfonamides and carbamates react to form 2,6-disubstituted piperidines, with the cis-isomer being the dominant, though not exclusive, product in both cases. As determined by 2D NOESY spectroscopy and 1D homonuclear decoupling experiments, the conformations of the *cis*-sulfonamide and carbamate products are different, with the alkyl groups of sulfonamide **35** existing in slightly distorted axial configurations on a chair structure and the alkyl groups of carbamate **36** being



35 **36**

FIGURE 2. Conformations of sulfonamide and carbamate products.



37

FIGURE 3. Andrachcinidine.

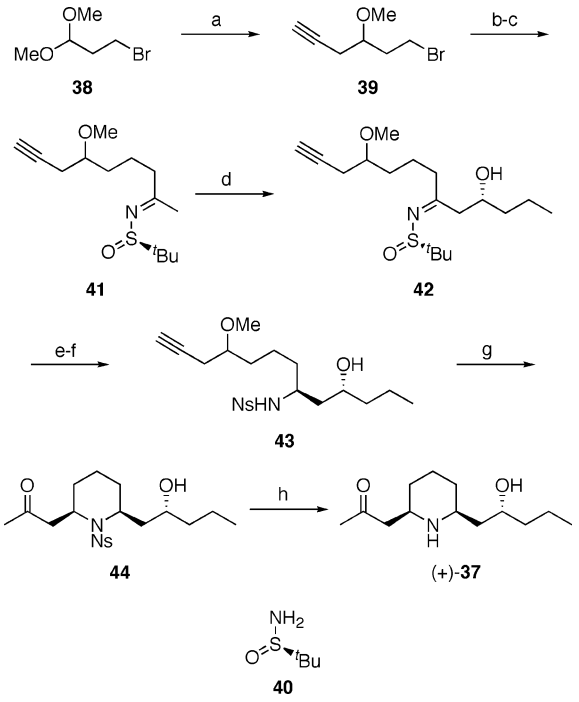
oriented by the half-chair ring conformation (Figure 2). An examination of related structures in the Cambridge Crystallographic Data Centre supported these conformational assignments. Thus, while the relative stereochemical outcomes of these reactions are not altered upon changing the group on nitrogen, the product conformations are substantially different. With respect to using this reaction for diversity oriented synthesis, the ability to access different substituent orientations through changing the group on nitrogen creates the opportunity to explore a greater range of conformational space with minimal effort.

Application to the Synthesis of (+)-Andrachcinidine. Andrachcinidine (**37**) is a piperidine-containing alkaloid from the beetle *Andrachne aspera* that has been implicated as a chemical defense agent (Figure 3).[34] Our ability to prepare 2,6-*cis*-dialkylpiperidine rings through the gold-mediated hydration/cyclization protocol led us to select **37** as a target for demonstrating the capacity of the method to be a key step in natural product total synthesis.

The synthesis of andrachcinidine is shown in Scheme 7. Lewis acid-mediated propargylation[35] of the commercially available acetal **38** with allenyl tributyltin[36] provided homopropargylic ether **39** in excellent yield. Displacement of the bromide with the metalloenamine derived from the cyclohexylimine of acetone[37] followed by condensing the resulting ketone with Ellman's sulfinamide **40**[38] provided sulfinylimine **41**. We selected this antipode of the auxiliary because it had previously been prepared in our group for a different purpose. While its use results in the synthesis of the enantiomer of the natural product, the antipodes of the sulfinamide are now equally accessible through an improved synthetic protocol.[39] Thus this sequence can be applied to the synthesis of the correct enantiomer of the natural product. Deprotonation of **41** with LDA, metal exchange with $MgBr_2$, and addition to *n*-butanal yielded alcohol **42**.[40] Reduction of the sulfinylimine with catecholborane[40] followed by a sequential protocol of acidic sulfinyl group cleavage, basification, and sulfonamide formation

(32) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121.
(33) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634.
(34) Mill, S.; Hootelé, C. *J. Nat. Prod.* **2000**, *63*, 762.
(35) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925.
(36) Tanaka, H.; Hai, A. K. M. A.; Ogawa, H.; Torii, S. *Synlett* **1993**, 835.
(37) Larchevêque, M.; Valette, G.; Cuvigny, T. *Tetrahedron* **1979**, *35*, 1745.
(38) (a) Liu, G.; Cogan, D.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
(39) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317.
(40) (a) Kochi, T. P.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518. (b) Kochi, T. P.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.

SCHEME 7. Total Synthesis of (+)-Andrachcinidine[a]

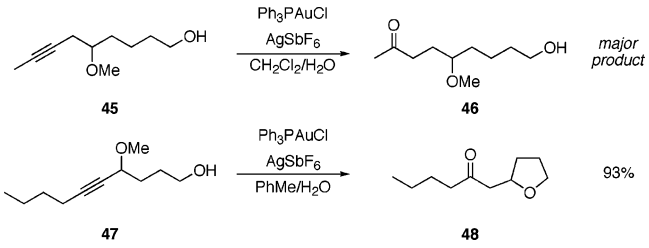


[a] Reagents and conditions: (a) allenyl tributyltin, $TiCl_4$, CH_2Cl_2, −78 °C, 93%; (b) acetone cyclohexylimine, LDA, THF, HMPA, −78 °C to rt, then H_3O^+, 41%; (c) **40**, $Ti(OEt)_4$, THF, 70 °C, 72%; (d) LDA, THF, then $MgBr_2$, then butyraldehyde, −78 °C, 65%; (e) catecholborane, THF, 0 °C, 78%, dr = 84:16; (f) HCl, MeOH, then NsCl, $NaHCO_3$, THF, H_2O, 83%; (g) Ph_3PAuCl, $AgSbF_6$, PhMe, H_2O, 40 °C, 24 h, 89% (h) PhSH, K_2CO_3, CH_3CN, 95%.

provided cyclization substrate **43**. Mosher ester analysis showed the enantiomeric excess of **43** to be 94%. The high enantiomeric purity can be attributed to the sulfinyl auxiliary promoting good diastereocontrol in both the aldehyde addition and reduction steps.[40] Exposing **43** to the standard cyclization conditions resulted in the formation of protected andrachcinidine (**44**) as a single diastereomer in 89% isolated yield. Direct cyclization of the sulfinylamide intermediate was unsuccessful due to the affinity of the sulfinyl group for the gold catalyst. Sulfonamide cleavage proceeded efficiently with basic thiophenol to yield the final product. Thus (+)-andrachcinidine can be prepared with excellent enantio- and diastereocontrol through a brief sequence in an 8% overall yield. This route compares quite favorably with the previously reported[41] synthesis of this compound.

Reactions with Internal Alkynes. All substrates in this report have been terminal alkynes. While this results in complete regiocontrol for the initial hydration reaction it limits the scope of the available products. Because of their exquisite nucleophilicity, metalated alkynes are highly versatile functional groups for fragment coupling in complex molecule synthesis. The ability to apply the mild gold-mediated cyclization conditions to internal alkynes would dramatically enhance the scope of products that can be accessed through the gold-mediated heterocycle synthesis. Applying the standard reaction conditions to internal alkyne **45** (Scheme 8), however, provided a mixture of products with the major pathway being simple alkyne hydration in which water reacted at the distal carbon with respect to the methoxy group

SCHEME 8. Cyclization with an Internal Alkyne Substrate



to yield ketone **46**. In contemplating approaches to controlling hydration regiochemistry, we became intrigued by Utimoto's results[21] in which propargylic ethers undergo hydration at the distal carbon with respect to the alkoxy group, ultimately leading to the formation of enones. Considering the presumed intermediacy of enones along our proposed mechanistic pathway, we turned our attention to the cyclization of propargylic ether **47**. Gratifyingly, exposing **47** to the standard cyclization protocol (procedure C) provided tetrahydrofuran **48** in 93% yield within 1 h. This result clearly demonstrates that internal alkynes can be used as substrates in this reaction and also indicates that any gold-mediated reaction that yields an α,β-unsaturated carbonyl group can potentially serve as an entry into heterocycle synthesis.[42]

Summary and Conclusions

We have developed a versatile and experimentally facile gold-mediated protocol for the synthesis of heterocyclic ketones from homopropargylic ethers. In these reactions hydroxyl, silyloxy, sulfonamide, and carbamate groups can serve as nucleophiles in the cyclization event. Mechanistic investigations indicated that the reaction pathway proceeds through alkyne hydration, alkoxy group elimination to form an enone, and nucleophilic addition. The reactions can be highly stereoselective when one diastereomer of the product is significantly more stable than the other because product stereoisomers interconvert under the reaction conditions. The method was applied to an efficient enantioselective synthesis of (+)-andrachcinidine that highlighted the capacity of the reaction to proceed without interference from a distal unprotected hydroxyl group. Our mechanistic proposal led us to employ a propargylic ether as a substrate, thereby expanding the scope of the reaction to include internal alkynes. This result suggests that gold-mediated protocols leading to the formation of an electrophilic alkene can be adapted to heterocycle synthesis.

Experimental Section

General Cyclization Procedure A. In a 2 dram (8 mL) screw-capped vial containing a magnetic stir bar was placed homopropargylic methyl ether and water-saturated CH_2Cl_2 (~60 mM final concentration). To the stirred solution at room temperature were added Ph_3PAuCl (5 mol %) and $AgSbF_6$ (5 mol %). The resulting white suspension was stirred at 35 °C until starting material consumption was complete. The black reaction mixture was dried over $MgSO_4$ and the crude contents of the vial in an ice bath were concentrated by using a N_2 gas. Products were purified by silica gel chromatography. For volatile products yields were determined by GC in accord with the procedure defined above.

(41) Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878.

(42) For an example of gold-mediated α,β-unsaturated ester formation, see: Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4207.

General Cyclization Procedure B. In a 2 dram (8 mL) screw-capped vial containing a magnetic stir bar was placed homopropargylic methyl ether and water-saturated CH_2Cl_2 (~60 mM final concentration). To the stirred solution at room temperature was added $NaAuCl_4 \cdot 2H_2O$ (5 mol %). The reaction mixture was stirred at 35 °C until starting material consumption was complete. The dark yellow reaction mixture was dried over $MgSO_4$ and the crude contents of the vial in an ice bath were concentrated by using a N_2 gas. Products were purified by silica gel chromatography. For volatile products yields were determined by GC in accord with the procedure defined above.

General Cyclization Procedure C. In a 4 dram (16 mL) screw-capped vial containing a magnetic stir bar was placed homopropargylic methyl ether and water-saturated toluene (~25 mM final concentration). To the stirred solution at room temperature were added Ph_3PAuCl (5 mol %) and $AgSbF_6$ (10 mol %). The resulting white suspension was stirred at 40 °C until starting material consumption was complete. The crude contents of the vial were directly purified by silica gel chromatography.

1-(1-(2-Nitrophenylsulfonyl)piperidin-2-yl)propan-2-one (31). General procedure C was followed with homopropargylic methyl ether **20** (50.0 mg, 0.147 mmol), Ph_3PAuCl (3.8 mg, 7.7 μmol), and $AgSbF_6$ (5.2 mg, 15 μmol) in water-saturated toluene (6.0 mL) for 12 h. The residue was purified by flash chromatography (20:1, CH_2Cl_2/EtOAc) to give **31** (41 mg, 84% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 1H), 7.67 (m, 3H), 4.46 (m, 1H), 3.78 (dm, J = 13.6 Hz, 1H), 3.00 (td, J = 13.6 Hz, 1H), 2.87 (dd, J = 16.7, 9.1 Hz, 1H), 2.70 (dd, J = 16.7, 4.3 Hz, 1H), 2.11 (s, 3H), 1.72−1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 147.7, 133.7, 133.4, 131.8, 131.2, 124.3, 49.2, 44.0, 41.8, 30.3, 28.1, 25.1, 18.3; IR (neat) 2944, 1716, 1544, 1342, 1372, 1160 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}N_2O_5SNa$ $(M + Na)^+$ 349.0834, found 349.0811.

6-Bromo-4-methoxyhex-1-yne (39). To a solution of 3-bromopropionaldehyde dimethyl acetal (**38**) (2.31 g, 11.4 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added allenyltributyltin (5.2 mL, 17. mmol), followed by the dropwise addition of $TiCl_4$ (13.6 mL, 1.0 M solution in CH_2Cl_2, 13.6 mmol). The dark brown mixture was stirred at −78 °C for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ at −78 °C and then was allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution. The crude material was extracted with EtOAc (2×). The combined organic phase was washed with brine (2×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20:1, hexanes/EtOAc) to afford **39** (2.10 g, 10.5 mmol, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (m, 3H), 3.43 (s, 3H), 2.45 (dd, J = 5.4, 2.7 Hz, 2H), 2.14 (m, 2H), 2.03 (t, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.1, 76.8, 70.5, 57.4, 37.1, 29.8, 22.8; IR (neat) 3298, 2931, 2828, 2120, 1433, 1360, 1260, 1109 cm^{-1}; HRMS (EI) *m*/*z* calcd for C_4H_9OBr $(M - C_3H_3)^+$ 151.9837, found 151.9824.

6-Methoxynon-8-yn-2-one. To a 1.0 M solution of LDA in THF (10 mL, 10 mmol) with HMPA (3.5 mL, 20 mmol) at −45 °C was added a cooled solution (−78 °C) of acetone cyclohexylimine[43] (1.40 g, 10.1 mmol) in THF (5 mL) dropwise. The yellow mixture was stirred at −45 °C for 1.5 h. To a solution of metalloenamine was added a cooled solution (−78 °C) of bromide **39** (1.58 g, 8.27 mmol) in THF (10 mL) dropwise. The resulting mixture was stirred at −45 °C for 2 h and allowed to warm to room temperature. The reaction mixture was then stirred at room temperature for 12 h. The reaction was quenched with water and acidified with 10% aqueous HCl solution at 0 °C (pH 6). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (4:1, hexanes/EtOAc) to afford ketone (573 mg, 3.41 mmol, 41%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.29 (m, 1H), 2.45 (t, J = 6.4 Hz, 2H), 2.39 (m, 2H), 2.12 (s, 3H), 1.98 (t, J = 2.6 Hz, 1H), 1.73−1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 80.8, 79.0, 70.0, 57.0, 43.6, 33.0, 29.8, 23.0, 19.6; IR (neat) 3287, 2933, 2827, 2118, 1715, 1427, 1360, 1160, 1112 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_7H_{13}O_2$ $(M - C_3H_3)^+$ 129.0915, found 129.0919.

(12*R*,*E*)-*N*-(6-Methoxynon-8-yn-2-ylidene)-2-methylpropane-2-sulfinamide (41). To a solution of the appropriate ketone (500 mg, 2.97 mmol) in THF (3 mL) was added $Ti(OEt)_4$ (3.10 mL, 14.9 mmol) at room temperature, followed by adding a solution of **40** (540 mg, 4.46 mmol) in THF (3 mL). The reaction mixture was stirred at 70 °C for 12 h. The reaction was cooled to 0 °C immediately and then poured into a brine solution with vigorous stirring. The resulting white suspension was filtered through a Celite pad and rinsed with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (10:1 to 4:1, hexanes/EtOAc with 5% Et_3N) to afford **41** (584 mg, 2.15 mmol, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.30 (m, 1H), 2.40 (m, 4H), 2.31 (s, 3H), 1.98 (t, J = 2.6 Hz, 1H), 1.67 (m, 4H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 80.8, 79.0, 70.0, 57.0, 56.2, 43.2, 33.0, 23.1, 22.9, 22.2, 21.3; IR (neat) 3469, 3294, 3235, 2928, 2826, 2118, 1624, 1475, 1362, 1189, 1112 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{14}H_{26}NO_2S$ $(M + H)^+$ 272.1684, found 272.1685.

(*R*,*Z*)-*N*-((4*R*)-4-Hydroxy-10-methoxytridec-12-yn-6-ylidene)-2-methylpropane-2-sulfinamide (42). To 1.0 M solution of LDA in THF (2.2 mL, 2.2 mmol) at −78 °C was added a cooled solution of **41** (502 mg, 1.85 mmol) in THF (8 mL). The mixture was stirred for 30 min and anhydrous $MgBr_2$ (670 mg, 3.70 mmol) was added in one portion. The mixture was stirred at −78 °C for 1 h. To the light yellowish metalloenamine solution was added *n*-butyraldehyde (0.25 mL, 2.8 mmol) dropwise. The reaction mixture was stirred at −78 °C for 24 h. After reaction was complete, a cooled 2.0 N solution of AcOH in THF (10 mL) was added dropwise and the resulting mixture was then stirred at −78 °C for 20 min. Brine and saturated aqueous $NaHCO_3$ solution were added and the reaction was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash chromatography (4:1 to 2:1, hexanes/EtOAc with 5% Et_3N) to afford **42** (410 mg, 1.19 mmol, 65%) as a colorless oil, which was immediately used for the next step because of the instability of **42**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (d, J = 9.4 Hz, 1H), 3.77 (m, 1H), 3.38 (s, 3H), 3.31 (m, 1H), 3.11 (t, J = 11.4 Hz, 1H), 2.40 (m, 4H), 1.99 (t, J = 2.5 Hz, 1H), 1.71−1.33 (m, 8H), 1.26 (s, 9H), 0.92 (t, J = 6.8 Hz, 3H).

(*S*)-*N*-((4*R*,6*S*)-4-Hydroxy-10-methoxytridec-12-yn-6-yl)-2-methylpropane-2-sulfinamide. To a solution of **42** (404 mg, 1.18 mmol) in THF (8 mL) at −50 °C was added catecholborane (0.38 mL, 3.5 mmol) dropwise. The reaction mixture was stirred at −50 °C for 2 h. MeOH (10 mL) and saturated aqueous sodium potassium tartrate solution (10 mL) were added. The resulting mixture was stirred for an additional 20 min and allowed to warm to room temperature. The white solution was washed with brine and extracted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude mixture was purified by flash chromatography (1:1, hexanes/EtOAc to 100% EtOAc) to afford pure *syn*-hydroxy sulfinamide (258 mg, 0.75 mmol, 64%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (m, 1H), 3.72 (m, 1H), 3.36 (s, 3H), 3.30 (m, 2H), 2.90 (dd, J = 6.8, 2.9 Hz, 1H), 2.39 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H), 1.80

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(m, 2H), 1.65−1.30 (m, 10H), 1.20 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.9, 79.0, 78.9, 71.5, 69.9, 57.0, 56.9, 56.8, 55.8, 43.1, 43.0, 40.9, 35.8, 35.7, 33.2, 23.0, 22.6, 21.6, 21.5, 18.5, 14.0; IR (neat) 3400 (br), 3311, 2932, 2870, 2119, 1645, 1457, 1364, 1106, 1043 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{35}NO_3SNa$ (M + Na)$^+$ 368.2235, found 368.2217; $[\alpha]^{23}_D$ −29.0 (c 0.700, $CHCl_3$).

***N*-((4*R*,6*S*)-4-Hydroxy-10-methoxytridec-12-yn-6-yl)-2-nitrobenzenesulfonamide (43).** To a solution of *syn*-hydroxy sulfinamide (246 mg, 0.71 mmol) in CH_3OH (10 mL) was added a 4.0 M HCl solution in 1,4-dioxane (0.36 mL, 1.42 mmol) at room temperature. The reaction mixture was stirred for 1 h. After the desulfinylation was complete, excess HCl and solvents were evaporated under reduced pressure. A mixture of THF/H_2O (v/v 1:1, 10 mL) was added, followed by the addition of $NaHCO_3$ (180 mg, 2.14 mmol) and 2-nitrobenzenesulfonyl chloride (181 mg, 0.85 mmol) at room temperature. The resulting mixture was stirred for 2 h. The crude mixture was extracted with EtOAc (2×). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1:2 to 1:1, hexanes/EtOAc) to afford **43** (252 mg, 0.59 mmol, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 1H), 7.85 (m, 1H), 7.73 (m, 2H), 5.52 (d, J = 7.3 Hz, 1H), 3.64 (m, 2H), 3.31 (s, 1.5H), 3.29 (s, 1.5H), 3.17 (m, 1H), 2.29 (m, 2H), 1.97 (m, 1H), 1.65−1.18 (m, 12 H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 135.0, 133.2, 132.7, 130.6, 125.2, 125.1, 80.8, 78.9, 78.8, 70.0, 69.3, 56.9, 53.6, 53.5, 42.6, 42.5, 40.1, 35.2, 33.2, 33.1, 23.0, 22.9, 18.5, 13.9; IR (neat) 3541, 3294, 3097, 2932, 2872, 2118, 1732, 1541, 1418, 1365, 1165 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{30}N_2O_6SNa$ (M + Na)$^+$ 449.1722, found 449.1699; $[\alpha]^{23}_D$ +26.2 (c 0.480, $CHCl_3$).

1-((2*R*,6*S*)-6-((*R*)-2-Hydroxypentyl)-1-(2-nitrophenylsulfonyl)-piperidin-2-yl)propan-2-one (44). To a solution of **43** (70.0 mg, 0.164 mmol) in water-saturated toluene (6.6 mL, 0.025 M) were added PPh_3AuCl (4.1 mg, 0.008 mmol) and $AgSbF_6$ (5.6 mg, 0.016 mmol). The reaction mixture was stirred at 40 °C for 24 h. The reaction solution was directly purified by chromatography on silica gel (10:1, CH_2Cl_2/EtOAc) to afford **44** (60.5 mg, 0.147 mmol, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 1H), 7.68 (m, 3H), 4.43 (ddm, J = 9.8, 3.2 Hz, 1H), 4.25 (m, 1H), 3.59 (m, 1H), 3.01−2.85 (m, 2H), 2.98 (dd, J = 16.5, 3.4 Hz, 1H), 2.89 (dd, J = 16.5, 9.8 Hz, 1H), 2.20 (s, 3H), 1.89 (ddd, J = 13.8, 9.3, 3.2 Hz, 1H), 1.83 (ddd, J = 13.8, 9.6, 4.2 Hz, 1H), 1.69 (d, J = 6.9 Hz, 1H), 1.65−1.34 (m, 10H), 0.95 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 147.7, 133.4, 131.9, 131.4, 124.5, 69.5, 50.1, 48.8, 48.1, 43.1, 40.5, 30.3, 27.7, 27.2, 18.8, 14.0, 13.3; IR (neat) 3400, 2955, 2871, 1714, 1544, 1373, 1340, 1168, 1136 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{23}N_2O_5S$ (M − C_3H_5O)$^+$ 355.1337, found 355.1328; $[\alpha]^{23}_D$ −44.0 (c 0.425, $CHCl_3$).

(+)-Andrachcinidine (37). To a solution of **44** (50.0 mg, 0.121 mmol) in acetonitrile (3.0 mL) were added K_2CO_3 (83.7 mg, 0.606 mmol) and thiophenol (37 μL, 0.36 mmol). The yellowish reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc to 10:1, EtOAc/methanol with 5% Et_3N) to afford (+)-**37** (26.3 mg, 0.116 mmol, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (m, 1H), 2.97 (dtd, J = 11.2, 6.3, 2.7 Hz, 1H), 2.74 (tt, J = 10.3, 2.5 Hz, 1H), 2.49 (dd, J = 16.5, 6.7 Hz, 1H), 2.43 (dd, J = 16.5, 5.8 Hz, 1H), 2.11 (s, 3H), 1.82 (dm, J = 13.5 Hz, 1H), 1.66 (dm, J = 13.1 Hz, 1H), 1.62 (dm, J = 13.1 Hz, 1H), 1.52 (m, 1H), 1.49 (m, 1H), 1.40 (m, 2H), 1.32 (m, 2H), 1.21 (dt, J = 14.2, 10.2, 1H), 1.08−0.96 (m, 2H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 72.5, 58.2, 53.0, 50.5, 43.1, 40.4, 33.5, 32.5, 30.6, 24.5, 18.6, 14.1; IR (neat) 3299 (br), 2929, 2859, 1713, 1457, 1360, 1107 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{25}NO_2$ (M$^+$) 227.1885, found 227.1882; $[\alpha]^{23}_D$ +24.1 (c 0.390, $CHCl_3$).

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Supporting Information Available: Experimental procedures for all cyclization reactions and spectral characterization of all cyclization starting materials, and products, and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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