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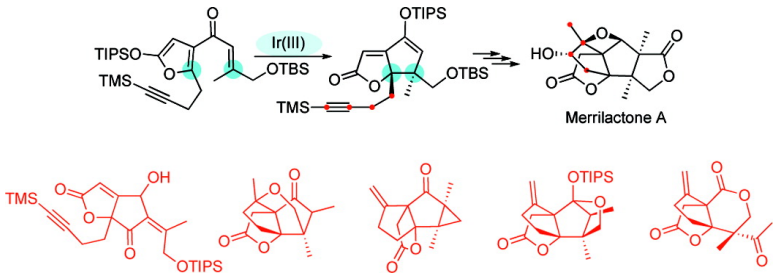

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Total Synthesis of (±)-Merrilactone A

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Abstract: The total synthesis of racemic merrilactone A (a neurotrophic agent) is described, featuring simultaneous and stereospecific creation of the C4 and C5 stereocenters via a notable silyloxyfuran Nazarov cyclization. Full details of the successful synthetic strategy are given, as well as several examples of the interesting reactivity of intermediates that were prepared and studied during the execution of the total synthesis. A detailed investigation of the Lewis acid-catalyzed Nazarov cyclization of silyloxyfurans was conducted, including a systematic study of substrate scope and limitations. In addition, experiments were conducted that suggest the participation of Lewis acidic silicon species in the Nazarov cyclization.

Introduction

Merrilactone A (**1**) was isolated from the pericarps of *Illicium merrillianum* in 2000 by Fukuyama and co-workers. The natural product exhibits unusual neurotrophic activity, promoting growth of fetal rat neurons at concentrations of 0.1 μmol/L.[1] The interesting structure of this small molecule has attracted the attention of synthetic groups because of its dense triquinane-like carbon skeleton, which contains seven contiguous chiral centers, of which three are quaternary. Danishefsky and Birman achieved the first total synthesis of (±)-merrilactone A, based on a Diels−Alder cycloaddition.[2] A year later, Inoue, Sato, and Hirama reported a strategy based on the ring contraction of a 1,4-cyclooctenediketone.[3] Both of these groups have also achieved asymmetric syntheses of merrilactone A,[4,5] and Inoue has synthesized the unnatural enantiomer of the natural product.[6] Mehta and Singh reported a third (racemic) synthesis based on the desymmetrization of 1,4-cyclopentenedione,[7] and other groups have also disclosed novel approaches to this unique carbocyclic system.[8,9]

The Nazarov cyclization is a 4π electrocyclization typically involving the conversion of divinyl ketones to cyclopentenones by activation with a Lewis acid (eq 1).[10] Conservation of orbital symmetry dictates a conrotatory cyclization pathway,[11] such that substrates with substituents at both termini of the pentadienyl cation intermediate will cyclize to generate adjacent stereocenters stereospecifically (see **II**→**III**, eq 1). However, often a stoichiometirc amount of a strong Lewis acid is necessary to promote cyclization, and the final stage of the cyclization involves the elimination of a proton from an oxyallyl cation intermediate (e.g., **III**) that often occurs with poor regioselectivity.[12]

Recently, catalytic protocols for Nazarov cyclization have been reported, using a wide range of transition-metal complexes. Our findings,[13] along with those of Trauner,[14] Tius,[15] Aggarwal,[16] and Occhiato,[17] indicate that polarization of the precursor divinyl ketone is key to the efficiency of these cyclizations. These studies, carried out by different research groups, have shown that compounds that develop high electron density at one terminus of the pentadienyl cation intermediate are particularly reactive and cyclize under mild conditions with ≤20 mol % of catalyst. For example, 1,2-dihydropyran-containing substrates readily undergo Lewis acid-catalyzed Nazarov cyclization[13−15] as well as regioselective elimination resulting from the asymmetry of the intermediate oxyallyl cation (eq 2).

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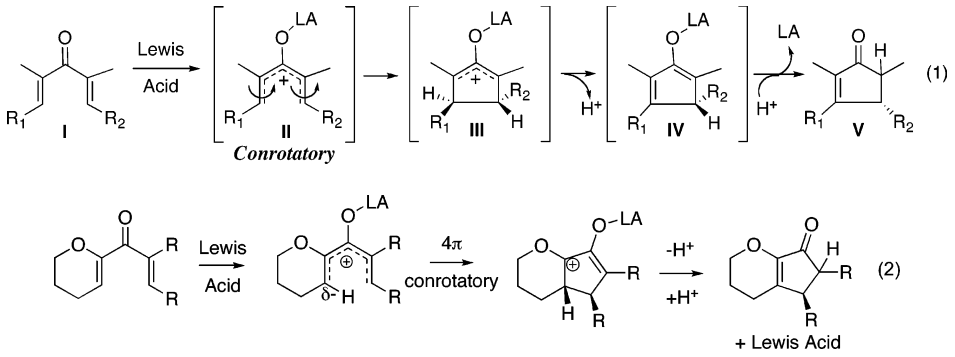
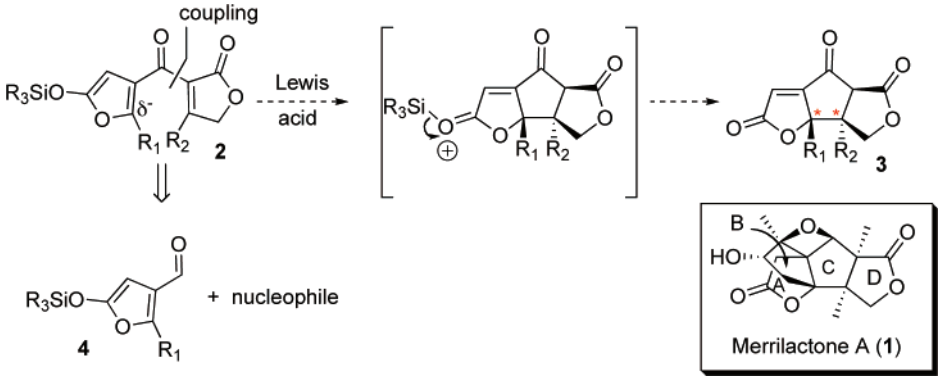


Scheme 1. Synthetic Plan Targeting Merrilactone A

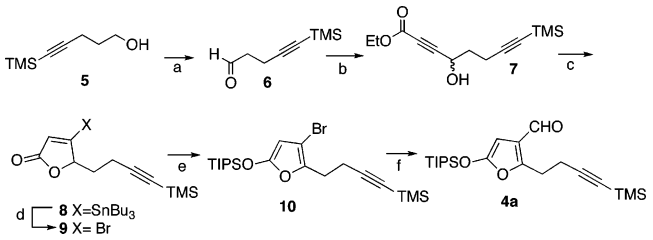


Like the dihydropyrans in eq 1, silyloxyfuranyl vinyl ketone **2** (Scheme 1) has high electron density at the 5-position of the furan. The intermolecular version of this reaction (Michael addition of trimethylsilyloxyfurans to α,β-unsaturated carbonyl compounds) is known,[18] and the reaction is also closely related to the catalytic asymmetric Michael reactions of silyl ketene acetals described by Evans et al.[19] These precedents indicate that a catalytic amount of a Lewis acid should trigger Nazarov cyclization of **2** to give tricyclic system **3**, which could be elaborated into the ACD ring system of merrilactone A. This interesting variation on the Nazarov cyclization would represent a general method to access [5,5]-fused butenolide ring systems containing adjacent stereocenters.

Results and Discussion

Initial Studies Targeting ACD Tricycle 3. Assembly of substrate **2** would require addition of an appropriate nucleophile to an aldehyde of type **4** (Scheme 1). Synthesis of ring A precursor **4a** started with known alcohol **5**[20] (Scheme 2), which was easily oxidized to aldehyde **6** in 90% yield. Treatment of **6** with a mixture of *n*-BuLi and ethyl propiolate at −78 °C gave alcohol **7** in 80% yield. Stannylcupration of the unprotected alkynoate proceeded smoothly,[21] and in situ cyclization occurred to afford desired lactone **8**. Bromination of **8** was carried out via titration in dichloromethane with a bromine solution at room temperature, affording **9** in 93% yield. The analogous iodination sequence was unselective: byproducts resulting from iodination

Scheme 2. Synthesis of Aldehyde **4a**[a]



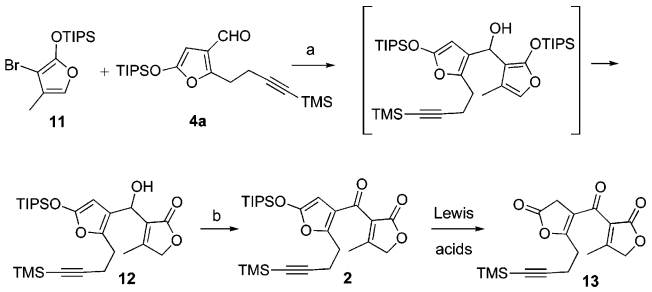
[a] Reaction conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −50 °C, 90%; (b) ethyl propiolate, *n*-BuLi, THF, −78 °C, then **6** 88%; (c) (Bu_3Sn)-$Cu(CN)Li_2$, THF, −78 °C, 90%; (d) Br_2, CH_2Cl_2, room temp, 93%; (e) TIPSOTf, Et_3N, CH_2Cl_2, −78 to 0 °C, quant; (f) (i) *t*-BuLi, ether, −78 °C; (ii) DMF, −78 to 10 °C, 79%.

of the alkyne were observed.[22] Treatment of **9** with triisopropylsilyl trifluoromethanesulfonate afforded the silyl furan ether **10** in nearly quantitative yield. Lithium-halogen exchange was achieved using 2 equiv of *t*-BuLi at −78 °C, and addition of DMF delivered target aldehyde **4a**, which could be stored at low temperature for months.

Despite a battery of coupling experiments targeting ketone **2**, the only productive result was achieved when the lithiofuran derived from bromide **11** was employed as the nucleophile (Scheme 3). Thus, treatment of **11**[23] with *t*-BuLi and addition of aldehyde **4a** gave **12** in 50% yield upon mild aqueous workup. The success of this coupling was surprising, and the selective hydrolysis may result from participation of the adjacent free hydroxyl group. Oxidation of **12** to the ketone **2** was readily achieved by Dess−Martin periodinane, although all other methods examined failed to give any desired product.[24] The ketone **2** was found to be relatively unstable, decomposing slowly even at low temperature.

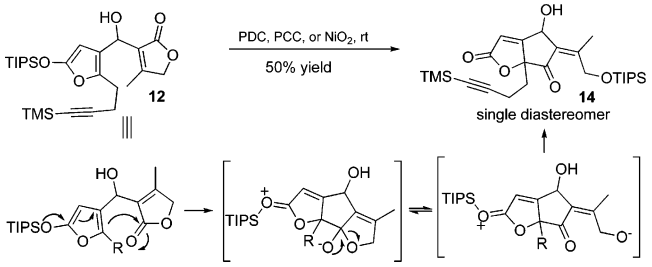
(18) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015.
(19) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, Michael C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.
(20) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699.
(21) (a) Reginato, G.; Capperucci, A.; Degl'Innocenti, A.; Mordini, A.; Pecchi, S. *Tetrahedron*, **1995**, *51*, 2129. See also: (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065.
(22) For the bromination/iodination protocol, see: Hollingworth, G. J.; Knight, J. R.; Sweeney, J. B. *Synth. Commun.* **1994**, *24*, 755.
(23) For the synthesis of **11**, see the Supporting Information.

Scheme 3. Synthesis and Attempted Cyclization of **2**[a]



[a] Reaction conditions: (a) **11**/*t*-BuLi, ether, −78 °C, then **4a**; mild aqueous workup; 50% yield; (b) Dess−Martin periodinane, CH_2Cl_2, room temp, 72%.

Scheme 4. Intramolecular Claisen Condensation of Alcohol **12**



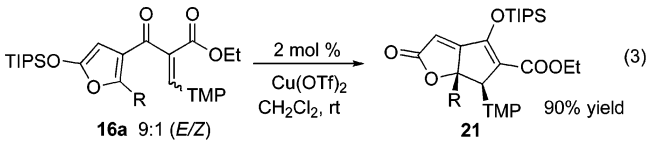
Unfortunately, attempts to effect Nazarov cyclization of **2** using a variety of Lewis acids, including $Cu(OTf)_2$, $TiCl_4$, $SnCl_4$, $AlCl_3$, TMSOTf, $FeCl_3$, and $ZnCl_2$, were unsuccessful. Butenolide **13** was the only product isolated.[25]

During attempts to oxidize the secondary alcohol **12** to the ketone **2**, an unexpected product was formed upon treatment with NiO_2, PDC, or PCC in dichloromethane. This compound was isolated in 50% yield. Treatment with D_2O led to the disappearance of one proton peak in ^1H NMR spectrum, indicating the presence of a hydroxyl group. The product was further characterized by ^{13}C, DEPT, and HSQC NMR spectroscopy, and the structure was assigned as the bicyclic ketone **14**.[26] Notably, only one diastereoisomeric product was isolated from these reactions, although the relative configuration of the product stereocenters was not determined.

Product **14** is thought to arise from an intramolecular Mukaiyama-type Claisen condensation, as shown in Scheme 4. To our knowledge, no other examples of this type of condensation have been reported previously. Given the high diastereoselectivity of the process and the complexity of the ring system formed, further development of this reaction for synthetic applications might be warranted.[27]

Catalytic Nazarov Cyclizations of Silyloxyfurans. When the cyclization of bicyclic silyloxyfuran **2** failed, alternative precursors to the merrilactone AC ring system were sought. In this regard, two types of acyclic substrates were examined: the simple enones of type **15**, and the alkylidene β-ketoesters of type **16** (Scheme 5). Alkylidene β-ketoester substrates **16** were easily prepared using a standard Knoevenagel condensation procedure.[28] Initially, it was thought that synthesis of enones of type **15** could be carried out as shown in Scheme 5 (top). Indeed, nucleophilic addition of the 4-lithiofuran derived from **10** or **17** to α,β-unsaturated aldehydes **18**[29] gave alcohol **19** with high efficiency.[30] However, oxidation to ketones **15** required treatment of **19** with a large excess of MnO_2[31] (50 equiv) in the presence of molecular sieves (4 Å) in dichloromethane at room temperature for 3 days,[32] and yields varied widely from substrate to substrate. Changes in temperature, solvent, and MnO_2 source did not improve efficiency, and yields dropped upon scaleup. Therefore, an alternative procedure employing Weinreb amides **20**[33] as electrophiles was developed to avoid the problematic oxidation of the secondary alcohol **19** (Scheme 5, bottom).[34]

Initial Nazarov cyclization attempts were carried out with silyloxyfuran **16a**, since earlier experiments showed that substrates bearing the 2,4,6-trimethoxyphenyl (TMP) substituent cyclize with great efficiency.[13] To our delight, $Cu(OTf)_2$ effected the cyclization of a 9:1 *E/Z* mixture of **16a**[35] to give 90% yield of [5,5]-fused butenolide **21**, containing adjacent stereocenters (eq 3). The stereochemistry of butenolide **21** corresponded to conrotatory cyclization of the minor (Z) isomer. It has been shown that E/Z isomerization of the alkylidene β-ketoester is facile under the reaction conditions and that the Z isomer cyclizes while the E isomer does not.[36]

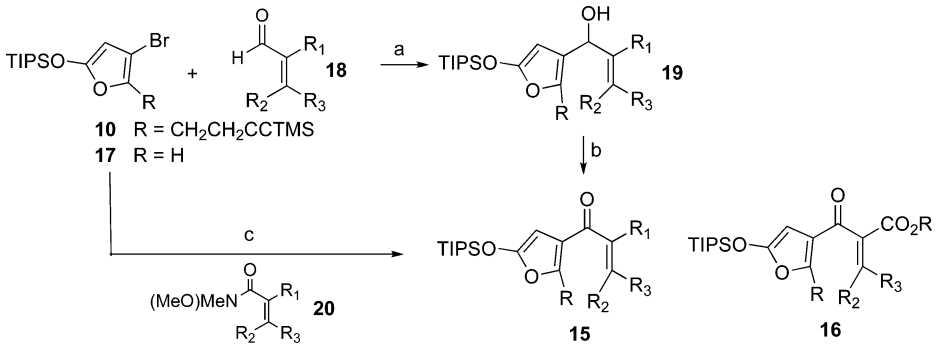


R = CH_2CH_2CCTMS; TMP= 2,4,6-trimethoxyphenyl

Unfortunately, although cyclization of substrate **16a** was successful, the cyclization of other related alkylidene β-ketoesters of type **16** did not occur with the same efficiency. Therefore, it was not surprising to find that copper triflate was not a competent catalyst for the cyclization of simple ketone **15a** (eq 4). However, we were pleased to find that cyclization was possible when the complex $Ir[(dppe)(CO)(DIB)(CH_3)]^{2+}$

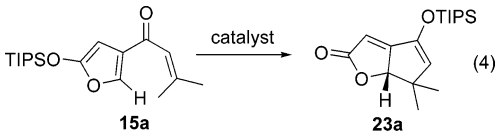
(24) Oxidation conditions examined included manganese dioxide, nickel dioxide, pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), TPAP/NMO, and Swern oxidation.
(25) Two related substrates were synthesized, and neither one cyclized. These results suggest that the alignment of the two olefin moieties for bicyclic substrates like **2** is poor. See Supporting Information.
(26) For details, see the Supporting Information.
(27) Many of the reagents that triggered the cyclization were oxidants, suggesting that an oxidative radical process may be a potential mechanism for the cyclization. Indeed, when the starting material was treated with tris(4-bromophenyl) hexachloroantimonate, a cationic radical promoter, the reaction proceeded smoothly and efficiently even at -78 °C. For another example of a Michael addition carried out under oxidative conditions, see: Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 2951.
(28) For experimental details, see the Supporting Information and the following: Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R.; Flaschenreim, C. *Tetrahedron* **2005**, *61*, 6193.
(29) For synthesis of aldehydes **18**, alcohols **19**, and enones **15** see Supporting Information. Initial experiments toward the synthesis of compound **18** were carried out by Dr. Patrick Caruana.
(30) Ishihara, J.; Yamamoto, Y.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387.
(31) Muehldorf, A. V. *Tetrahedron Lett.* **1994**, *35*, 6851.
(32) Dess−Martin oxidation, Swern oxidation, TPAP oxidation, Parikh−Doering (SO_3·Py) oxidation, pyridinium dichromate (PDC), pyridinium chlorochromate (PCC), $BaMnO_4$, and NiO_2 did not achieve the desired oxidation of **19** to **15.**
(33) For synthesis of the Weinreb amides, see the Supporting Information.
(34) For a single example of the successful coupling of a 4-lithiofuran with a Weinreb amide, see Kanoh, N.; Ishihara, J.; Yamamoto, Y.; Murai, A. *Synthesis*, **2000**, *13*, 1878. The procedure presented in Scheme 5 was employed in the synthesis of several Nazarov substrates (see Supporting Information).
(35) Assignment of olefin geometry was made by J^3 C-H coupling: Kingsbury, C. A.; Draney, D.; Sopchik, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 3863. The ratio of isomers was determined by ^1H NMR.
(36) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.*, in press.

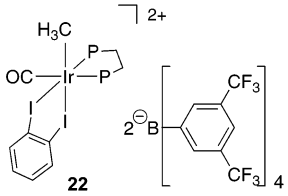
Scheme 5. Synthesis of Enone Nazarov Substrates **15**[a]



[a] Reaction conditions: (a) **10** or **17**/*t*-BuLi, ether, −78 °C, then **18**; 40−82% yield; (b) MnO_2 (50 equiv), mol. sieves, CH_2Cl_2, room temp (34−69% yield); (c) **10** or **17**/*t*-BuLi, ether, then **20**; −78 °C to room temp, 68−83% yield.

2 BAr^{f-} (**22**) was the catalyst,[37] even though **15a** is missing the TMP group *and* the ester that is usually involved in two-point complexation to the catalyst.[37,38]





22

$Cu(OTf)_2$ (10 mol%) : *no cyclization*
Ir(III) complex **22** (2 mol%, CH_2Cl_2, rt): 67% yield.

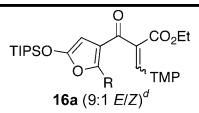
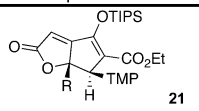
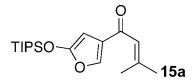
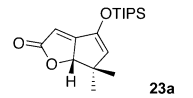
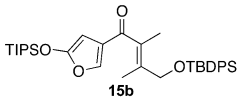
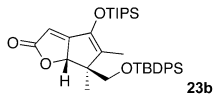
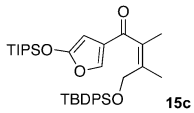
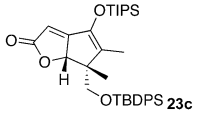
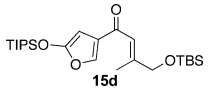
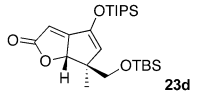
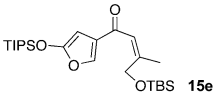
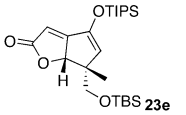
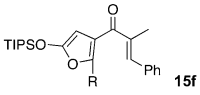
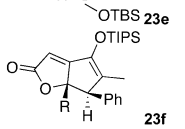
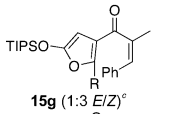
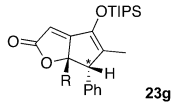
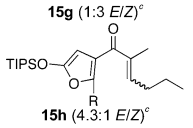
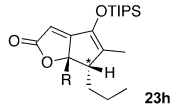
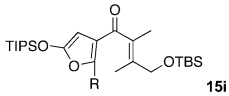
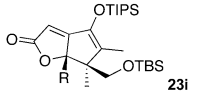
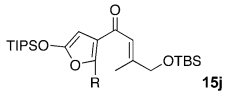
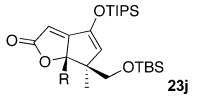
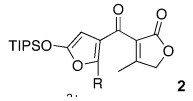
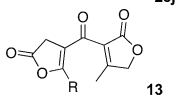
A series of other ketones of type **15** also underwent smooth cyclization with catalyst **22** (Table 1). Cyclization of the original alkylidene β-ketoester **16a** could also be effected with Ir(III) complex **22**, with efficiency comparable to the Cu(II) case (entry 1). Tetrasubstituted enones cyclized to give tetrasubstituted enol silane products bearing a quaternary center (entries 3−4), and substrates with γ-substitution on the silyloxyfuran also cyclized efficiently (entries 7−12). As expected, the geometry of the starting enone was converted directly into the stereochemistry of the product butenolides **23** via conrotatory cyclization.[11,39] In this way, cyclization of pairs of geometric isomers led to the synthesis of pairs of cyclopentenyl diastereomers (entries 3 vs 4, 5 vs 6, and 7 vs 8). Cyclization occurs even when steric hindrance is significant: note the congestion of the adjacent stereocenters formed in entries 10 and 11. However, attempts to construct a tricyclic structure utilizing this strategy were not successful (entry 12; see also Scheme 3). It is possible that when the rigid lactone unit engages in two-point chelation with the Lewis acid catalyst, the system is unable to achieve the orbital overlap necessary for cyclization.[25] *tert*-Butyldimethylsilyloxyfurans also cyclized, albeit in poor yield. These results were attributed to poor stability of both the substrate and the enol silane product.

In these Nazarov cyclizations, the triisopropylsilyl group is transferred from the silyloxyfuran to the ketone oxygen during the reaction, a process analogous to the silicon transfer step that characterizes the Mukaiyama−Michael addition.[40] Since electrophilic trialkylsilyl species are known to catalyze both Mukaiyama−Michael reactions[41] and Nazarov cyclizations,[42] it was necessary to investigate the possibility that a Lewis acidic silicon species formed in situ could be competing with the Ir-(III) catalyst.[43] A series of experiments indicated that TIPSOTf did not catalyze the cyclization of any silyloxyfuranyl substrate. To more closely duplicate the silylium species that might be formed in situ in the presence of the $Ir(III)^{2+}$ $2BAr^{f-}$ complex, $NaBAr^f$ was mixed with TIPSOTf, a procedure that is expected to precipitate NaOTf[45] and give the ion pair $TIPS^+ \cdot BAr^{f-}$.[46] The suspension was filtered to remove NaOTf, and the resultant solution was added to substrate **15a** in dichloromethane. Cyclization was rapid and efficient, which was an interesting result given the unusual nature of the triisopropylsilylium cation.[46] Furthermore, the results from the "silyilium" cyclization were identical to the results of cyclizations catalyzed by Ir(III) complex **22**, which calls into question the true identity of the catalyst for these silyloxyfuran cyclizations.[47] While these kinds of poorly defined Lewis acidic trialkylsilyl-BAr^f species are not typically used as catalysts for organic reactions, the related silyl triflimides $R_3Si \cdot NTf_2$ are known to be highly efficient catalysts for Mukaiyama aldol[48] and Mukaiyama−Michael reactions.[49] Indeed, 1 mol % of either $TBS \cdot NTf_2$ or $TIPS \cdot NTf_2$ also led to efficient cyclization of triisopropylsilyloxyfuran **15a**.

These studies represent the development of an efficient, catalytic Nazarov cyclization of trialkylsilyloxyfuranyl ketones. The results suggest that while Ir(III) complex **22** was initially thought to be the catalyst for the reaction, it appears likely that a Lewis acidic silicon species is also involved in the process.

(37) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864.
(38) See reference 28.
(39) Stereochemistry of products was determined by 1D nOe experiments.
(40) (a) Narasaki, K.; Soai, K.; Mukaiyama, T.; *Chem. Lett.* **1974**, 1223. (b) Saigo, K.; Otsuki, M.; Mukaiyama, T. **1976**, *5*, 163.
(41) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.
(42) Andrews, J. F. P.; Regan, A. C. *Tetrahedron Lett.* **1991**, *32*, 7731.
(43) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. (b) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. (d) Hiraiwa, Y.; Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 1827.
(44) Ref deleted in proof.
(45) Arndtsen, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970.
(46) Lambert, J. B.; Zhang, S.; Stern, C. L.; Huffman, J. C. *Science* **1993**, *260*, 1917.
(47) No reaction occurred in the presence of $NaBAr^f$ alone, indicating that the silicon species was responsible for the catalytic cyclization. See Supporting Information.
(48) (a) Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127. (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.
(49) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668.

Table 1. Nazarov Cyclization of Type **15** and **16** Silyloxyfurans with Ir(III) Catalyst **22**[a]

entry	substrate[b]	product	yield (%)
1	 **16a** (9:1 *E*/*Z*)[d]	 **21**	90
2	 **15a**	 **23a**	67
3	 **15b**	 **23b**	84
4	 **15c**	 **23c**	77
5	 **15d**	 **23d**	65
6	 **15e**	 **23e**	78
7	 **15f**	 **23f**	90
8	 **15g** (1:3 *E*/*Z*)[c]	 **23g**	78[d]
9	 **15h** (4.3:1 *E*/*Z*)[c]	 **23h**	63[e]
10	 **15i**	 **23i**	93
11	 **15j**	 **23j**	82
12	 **2**	 **13**	74[f]

[a] Reaction conditions: $Ir[(dppe)(CO)(DIB)(CH_3)]^{2+}$ 2 BAr^{f-} (2 mol %), CH_2Cl_2, room temperature. [b] R= CH_2CH_2CCTMS. [c] Inseparable mixture of olefin isomers.[35] [d] Obtained in a 1:3.2 mixture of diastereomers about the H/ Ph stereocenter; the major diastereomer observed was **23g**. [e] Obtained in a 1:3 mixture of diastereomers about the H/ *n*-propyl stereocenter; major diastereomer observed was **23h**. [f] Other Lewis acids such as $Cu(OTf)_2$ and $AlCl_3$ and Ir(III) gave comparable results.

Further experimentation is necessary to determine whether Ir-(III) complex **22** is able to both initiate and catalyze cyclization or that it simply initiates catalysis by a Lewis acidic silicon species. The methodology provides rapid, stereospecific access to [5,5]-fused butenolide-containing systems with adjacent stereocenters.

With AC ring system **23i** in hand, attempts were again made to synthesize the tricyclic ACD system **3** (Scheme 6). Selective deprotection of the primary silyloxy group of **23i** and subsequent conversion to the carbonate derivative would set the stage for intramolecular acylation, in order to install lactone ring D with the necessary *cis*-[5,5] ring fusion. Unfortunately, compound **23i** decomposed rapidly upon exposure to several different fluoride-containing reagents. It was remarkably stable under acidic conditions but, despite extensive experimentation, selective deprotection could not be achieved.

Construction of the ABC Tricycle 26 from Nazarov Cyclization Product 23i. Because assembly of the ACD system was problematic, a strategy involving construction of ring B prior to deprotection of **23i** was pursued (Scheme 7). Deprotection of the TMS group of **23i** was best achieved by treatment of $AgNO_3$ and KCN, providing terminal alkyne **24**.[50] Radical cyclization proceeded smoothly with azobis(isobutyronitrile) (AIBN) and tributyltin hydride (Bu_3SnH)[51] to give vinylstannane **25** in high yield (88%) along with a trace amount ($\sim$ 4%) of the target *exo*-olefin **26**. Addition of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) in benzene to the reaction effected conversion of remaining vinylstannane **25** to **26** in situ. A trace amount of the free alcohol **27**, arising from the deprotection of the *tert*-butyldimethylsilyl (TBS) group, was also isolated.

Tricycle **26** contained all the carbon atoms of the merrilactone A carbon skeleton except C-12. To explore intramolecular acylation procedures, it was necessary to selectively deprotect the primary alcohol. Since *p*-TsOH·H_2O was observed to effect the partial deprotection of the *tert*-butyldimethyl (TBS) group during the cyclization sequence (Scheme 7), we chose first to explore this avenue. After extensive optimization, it was found that treatment of **26** with 4 equiv of *p*-TsOH·H_2O in ethanol for 4 h furnished the desired primary alcohol **27** in 40% yield, along with recovered **26** (40%) and the acetal **28** (15%) (Scheme 8). Longer reaction times led exclusively to acetal **28**.

Consistent with the observations noted above, primary alcohol **27** was found to be unstable under both aqueous workup conditions and on silica, forming acetal **28** as a single diastereomer in less than 10 min in both cases. Global deprotection attempts resulted in efficient formation of acetal **28**, which proved inert to hydrolysis with *p*-TsOH·H_2O even after long reaction times at elevated temperatures. However, subjection of compound **26** to similar forcing conditions triggered oxycyclization, affording ether **30** in low yield. The fully deprotected hydoxyketone was not observed in either case (Scheme 8).

The structure of ether **30** was assigned by ^1H, ^{13}C, and 2D-COSY NMR spectroscopy (see Supporting Information). The structure and stereochemistry of acetal **28** were unambiguously established by X-ray crystallography (Figure 1).[52] The C-3 (C-7 in the X-ray structure) side chain and the C-11 (C-12 in the X-ray structure) side chain had the expected syn relationship predicted from the Nazarov cyclization and required for synthesis of merrilactone A.

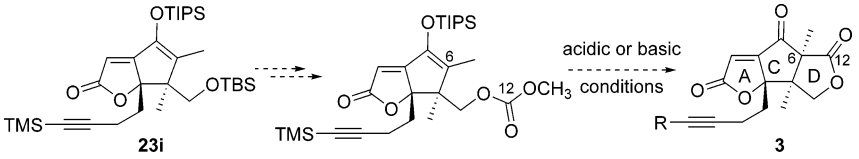
Fortunately, 1 equiv of TBAF effected the selective deprotection of the triisopropylsilyl (TIPS) group at -78 °C to give the *tert*-butyldimethylsilyl (TBS) protected hydroxy ketone **31** (Scheme 9). If excess TBAF was used, global deprotection was achieved to yield hydroxyketone **29**. As was observed in the

(50) Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.* **1990**, *55*, 5324. A variety of fluoride-based deprotection reagents such as TBAF, HF, and HF·Py were unselective, and no reaction occurred using K_2CO_3 in methanol.

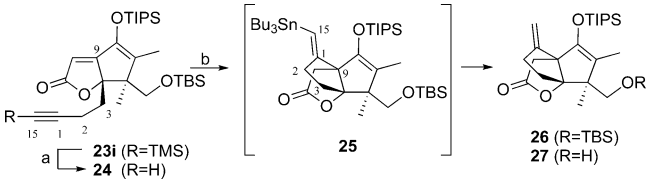
(51) Shanmugam, P.; Srinivasan, R.; Rajagopalan, K. *Tetrahedron*, **1997**, *53*, 6085.

(52) With the exception of the numbering that appears in Figures 1 and 2 (assigned for the purposes of X-ray analysis only), the carbon numbering in the manuscript will correspond to the numbering of the natural product merrilactone A (see ref 1).

Scheme 6. Proposed Construction of ACD Tricycle **3** via Intramolecular Acylation

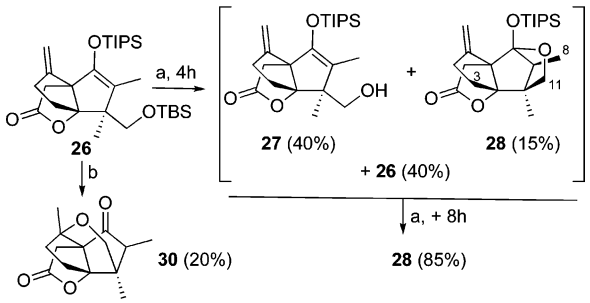


Scheme 7. Radical Cyclization of Terminal Alkyne **24**[a]



[a] Reaction Conditions: (a) $AgNO_3$, then KCN, THF/H_2O/EtOH, 93%; (b) (i) AIBN, Bu_3SnH, PhH, reflux, then (ii) *p*-TsOH·H_2O (one pot), 88% (**26**), 4% (**27**).

Scheme 8. Treatment of **26** with *p*-TsOH·H_2O[a]



[a] Reaction conditions: (a) *p*-TsOH·H_2O, EtOH, room temp; (b) *p*-TsOH·H_2O, benzene, reflux, 2 h.

formation of acetal **28**, both **29** and **31** were obtained as single diastereomers (rather than as pairs of C-6 epimers), although it was not possible to assign the C-6 stereochemistry with confidence.

Thus, after extensive experimentation, conditions were identified that allowed selective deprotection of either silyl group of **26** or its global deprotection (Schemes 8 and 9).

Efforts To Form the ABCD Tetracycle from Derivatives of 26. Encouraged by literature examples of lactone formation

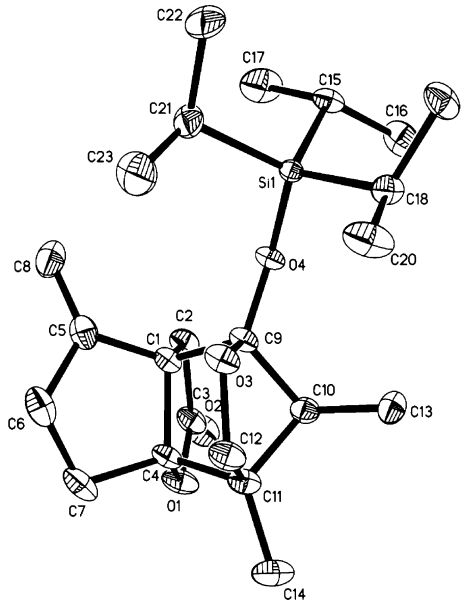
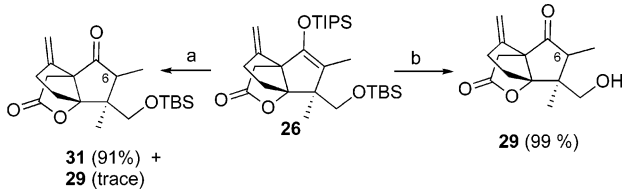


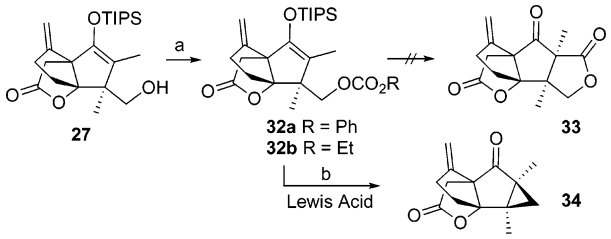
Figure 1. X-ray structure of TIPS acetal **28**.

Scheme 9. Selective Deprotection of **26** with Tetrabutylammonium Fluoride[a]



[a] Reaction conditions: (a) TBAF (1 equiv), THF, −78 °C; (b) TBAF (3 equiv), THF, room temp.

Scheme 10. Attempted Intramolecular Acylation of Carbonates **32**[a]



[a] Reaction conditions: (a) LDA, $ClCO_2R$, 90%; (b) TMSOTf (72%), $TiCl_4$, or BF_3·Et_2O.

via acylation of ketone enolates with pendant carbonates,[53] it seemed possible that the TIPS enol ether might be nucleophilic enough to allow direct acylation with carbonates of type **32** to give desired tricycle **33** (Scheme 10). Carbonate substrates **32a** and **32b** were prepared by acylation of primary alcohol **27**. LDA was found to be the ideal base for these reactions, while nucleophilic bases such as 4-dimethylaminopyridine (DMAP) or *n*-BuLi yielded primarily TIPS acetal **28**. Since this transformation is similar to the Mukaiyama aldol reaction, in the sense that an enol ether attacks a Lewis acid activated carbonyl electrophile to form a new carbon−carbon bond,[54] Lewis acidic conditions were explored first. In a surprising twist, attempted acylation of phenyl carbonate **32a** using TMSOTf as the Lewis acid promoter led to exclusive formation of cyclopropane **34**. No lactone product **33** was detected. The same result was observed with ethyl carbonate **32b**, and with alternative Lewis acids $TiCl_4$ and BF_3·Et_2O.

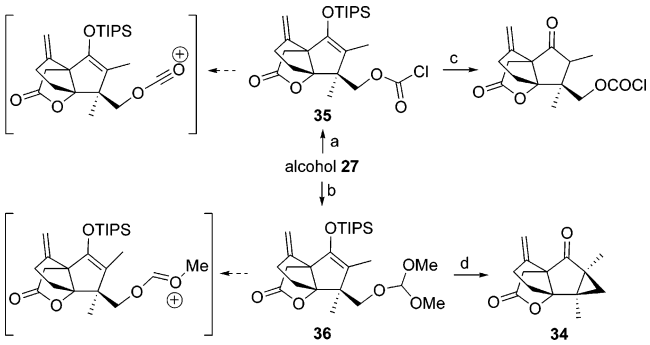
When carbonates **32** underwent S_N2-type displacement instead of acylation, alternative C-12 carbon donors were sought. Chloroformate **35** and orthoester **36** were appealing because both were expected to collapse to reactive oxonium ions upon treatment with a Lewis acid (Scheme 11).[55] The acylation could

(53) (a) Goldsmith, D. J.; John, T. K.; Van Middlesworth, F. *Synth. Commun.* **1980**, *110*, 551. (b) Molander, G. A.; Quirmbach, M. S.; Silva, L. F.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *15*, 2257. (c) Cho, S. Y.; Carcache, D. A.; Tian, Y.; Li, Y.; Danishefsky S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358.

(54) However, the reaction between a silyl enol ether and carbonate, either in an intermolecular fashion or in an intramolecular fashion, had not been reported.

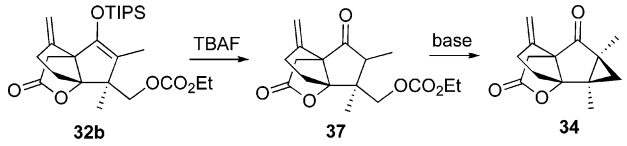
(55) Activation of orthoformates with Lewis acids has been reported to give electrophilic species that are reactive toward C=C double bonds: Li, T. T.; Lesko, P.; Ellison, R. H.; Subramanian, N.; Fried, J. H. *J. Org. Chem.* **1981**, *46*, 111.

Scheme 11. Cyclization Experiments with Chloroformate **35** and Orthoformate **36**[a]



[a] Reaction conditions: (a) phosgene, CH_2Cl_2 90%; (b) $HC(OMe)_3$, $MgCl_2$, CH_2Cl_2; (c) TMSOTf or AgOTf, 88%; (d) $TiCl_4$, 68% (from **27**).

Scheme 12. Attempted Intramolecular Acylation under Basic Conditions[a]



[a] Bases examined: *n*-BuLi, LDA, NaH, NaOMe, NaH/KH, KH, KO^{t}Bu.

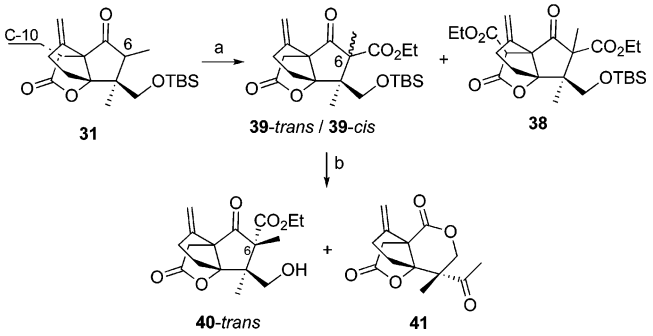
then proceed via a *5-exo* reaction pathway, with less steric congestion at the site of the C-6/C-12 bond formation. As shown in Scheme 11, both precursors could be prepared in one step from alcohol **27**.[56,57]

The results of these cyclization attempts were disappointing, however. Treatment of chloroformate **35** with promoters TMS·OTf and AgOTf only triggered hydrolysis of the triisopropylsilyl (TIPS) enol ether. No cyclization was observed. Treatment of unstable orthoformate **36** with $TiCl_4$ gave cyclopropane **34** in good yield as the exclusive product of the reaction.

These experiments provided strong evidence that the Lewis acid-mediated acylation of triisopropylsilyl (TIPS) enol ether was not a viable strategy for the synthesis of lactone **33**. Acylation of the corresponding enolates, expected to be smaller and more reactive, was pursued next. The first experiment, treatment of carbonate **32b** with fluoride ion under basic conditions, gave ketone **37** at −78 °C (90% yield) and formation of cyclopropane **34** at 0 °C (66% yield; Scheme 12). Formation of the enolate from ketone **37** in the presence of metals that might be able to coordinate both the ketone oxygen and the carbonyl oxygen of the carbonate was also explored to encourage proper alignment of the nucleophile and the electrophile. However, deprotonation of **37** always gave cyclopropane **34**, sometimes along with the hydroxyketone **29**.

In a final effort to build ring D onto an intermediate derived from intermediate **26**, *intermolecular* acylation of α-methyl ketone **31** was investigated. Although the stereoselectivity of acylation at C-6 was expected to be poor, any opportunity to access desired lactone **33** had become attractive. Upon initiation of these experiments, it was found that excess LDA was required to drive the acylation of **31** with ethylchloroformate to completion. However, a byproduct tentatively assigned as C-10 acylated lactone **38** was always formed under these conditions (Scheme 13). Fortunately, it was possible to isolate a mixture of diastereomeric ketoesters **39** (trans and cis) in 67% combined yield. ^{1}H NMR revealed a 2.3:1 ratio of epimers, but relative stereochemistry could not be assigned from the spectrum. Exposing the mixture of ketoesters **39** to TBAF led to the formation of two new products. One of them was confidently assigned as the hydroxy ketoester **40**-*trans*, which was expected to be inert under lactonization conditions owing to the trans relationship of the alcohol and the ester. The other product was assigned as γ-butyro-δ-valerolactone **41**, via X-ray crystallographic analysis (Figure 2).[52]

Scheme 13. Intermolecular Acylation of Ketone **31**[a]



[a] Reaction Conditions: (a) LDA (1.8 equiv), $ClCO_2Et$ (1.5 equiv) gave **38** (∼15% yield) and diastereomers **39** (2.3:1 ratio, 67% yield); (b) TBAF, THF, 0 °C to room temp; gave **40**-*trans* (57% yield) and **41** (26% yield).

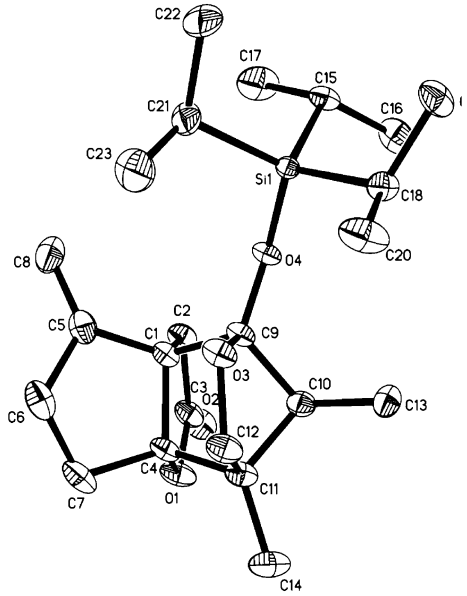
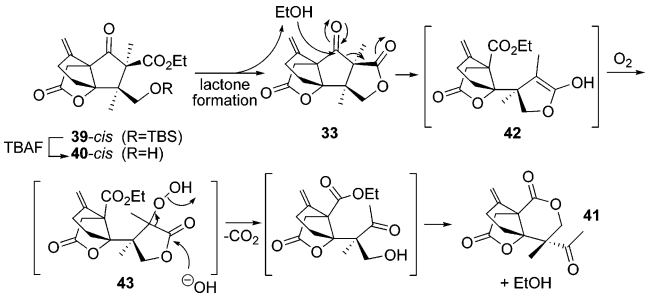


Figure 2. X-ray crystal structure of compound **41**.

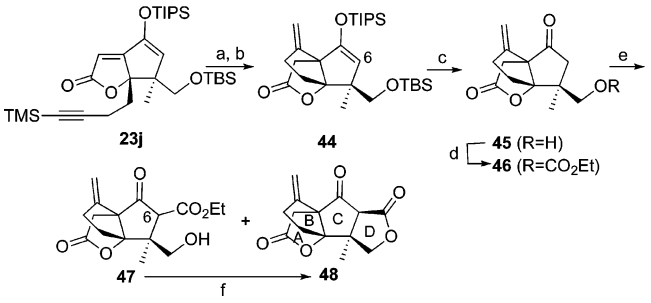
Isolation of **40**-*trans* from the reaction mixture suggests that only **39**-*cis* undergoes the rearrangement/fragmentation. An oxidation event must also occur to deliver product **41**, probably via the action of adventitious oxygen in the reaction mixture.[58] A possible mechanistic pathway for the transformation is shown in Scheme 14. TBAF should effect deprotection of the silyl ethers **39** to afford primary alcohols **40**. Alcohol **40**-*cis* could then undergo lactonization as planned to give the elusive product **33**, generating a molecule of ethanol. It is then possible that

(56) Chloroformate: Lucas, M. A.; Schiesser, C. H. *J. Org. Chem.* **1996**, *61*, 5754.
(57) Orthoester: Perron, F.; Gahman, T. C.; Albizati, K. F. *Tetrahedron Lett.* **1988**, *29*. 2023.
(58) (a) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578. (b) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (c) Gardner, J. N.; Popper, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. L. *J. Org. Chem.* **1968**, *33*, 3695−3699.

Scheme 14. Proposed Mechanism of the Formation of the δ-Valerolactone **41**



Scheme 15. Formation of Ring D via Intramolecular Acylation[a]



[a] Reaction Conditions: (a) $AgNO_3$, then KCN, THF/H_2O/EtOH, 87%; (b) (i) AIBN, Bu_3SnH, PhH, reflux, then (ii) *p*-TsOH·H_2O (one pot), 91%; (c) 3 equiv TBAF, 0 °C, 99%; (d) DMAP, Py, $ClCO_2Et$, 95%; (e) 20 equiv NaH, THF, **47**:**48** = 1:1; (f) *p*-TsOH·H_2O (90% from **46**).

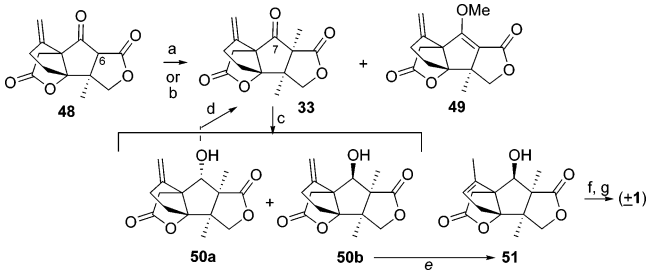
α,α-disubstituted β-ketoester **33** undergoes ring opening via attack by either ethanol or water present in the TBAF solution to give intermediate **42**. Autoxidation of **42**[59] would give α-hydroperoxide **43**, which could then fragment and lactonize as shown to deliver **41**.

These experiments demonstrated that intermolecular acylation of α-methyl ketone **31** is also not a viable approach to the synthesis of merrilactone A, so again, alternative routes were sought.

Completion of the Synthesis from Nazarov Cyclization Product 23j. Given the disappointments experienced during attempts to form ring D via acylation of derivatives of tetrasubsituted silyl enol ether **26**, an alternative strategy involving acylation of the less hindered C-6 carbon of trisubsituted silyl enol ether **44** was considered (Scheme 15). This approach was promising because the two examples of intramolecular acylation previously reported involved α-unsubstituted ketones.[53] To this end, the chemistry developed for ring ABC formation from **23i** (cf. Scheme 7) was carried out on **23j** (Table 1, entry 11) delivering **44** without complication. Deprotection with 3 equiv of TBAF delivered ketone **45** in good yield, and the DMAP/Py/$ClCO_2Et$ protocol reported by Molander gave target carbonate **46**.[53b] Finally, treatment of **46** with excess NaH in THF triggered intramolecular nucleophilic lactonization[53c] to give a 1:1 mixture of the desired lactone **48** along with a single diastereomer of β-ketoester **47** (relative stereochemistry at C-6 was not determined). Subsequent treatment of this mixture with *p*-TsOH·H_2O converted **47** cleanly into **48**, furnishing the desired bislactone **48** in 90% yield from carbonate **46**. Incredibly, no cyclopropanation was observed in this reaction.

(59) (a) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578. (b) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (c) Gardner, J. N.; Popper, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. L. *J. Org. Chem.* **1968**, *33*, 3695.

Scheme 16. Completion of the Total Synthesis[a]



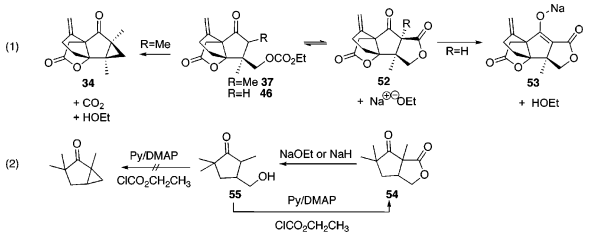
[a] Reaction Conditions: (a) NaH, MeI, gave **33** (84% yield) and **49** (14% yield); 6:1 ratio; (b) NaH, MeI, and then HMPA, gave **33** only (97% yield); (c) $NaBH_4$, MeOH gave **50a** (42% yield) and **50b** (51% yield); (d) Dess−Martin periodinane (99% yield);(e) *p*-TsOH·H_2O, benzene, reflux, 4 h, 92% yield; (f) *m*-CPBA; (g) *p*-TsOH·H_2O, 68% yield over two steps.

These experiments indicate that while cyclization of carbonate **46** gives exclusively lactone **48**, the analogous cyclization of C-6 methyl substituted analogue **37** gave only cyclopropane **34** (see Scheme 12). Evidently, the steric influence of the C-6 methyl in **37** was significant enough to completely change the course of the reaction.[60]

The final steps of the total synthesis were carried out as shown in Scheme 16. Installation of the C-6 methyl was first attempted by treatment of **48** with NaH and MeI. The reaction was sluggish and gave a 1:6 ratio of the O-methylation product **49** to the desired C-methylation product **33**. Fortunately, addition of HMPA both accelerated the reaction and delivered **33** in 97% yield.[61] Reduction of the C-7 ketone was unselective, which was not surprising given that the two hydride-accepting faces appeared to be equally accessible. Of the reducing agents examined, DIBAL-H and L-selectride appeared to overreduce **33**, while $NaBH_4$ effected exclusive albeit unselective reduction of the ketone. Fortunately, the reduction was achieved in high yield and the two alcohols **50a** and **50b** could be separated by chromatography. Undesired alcohol **50a** could then be oxidized back to the starting ketone **33** in quantitative yield using Dess−Martin periodinane. This recycling process enabled us to convert **50a** into the desired alcohol **50b** in 73% yield after two cycles.

Isomerization of **50b** by treatment with *p*-TsOH·H_2O in refluxing benzene for 4 h furnished Danishefsky's intermediate **51**. Finally, following the procedures of Danishefsky and

(60) A reversible Dieckmann condensation process could also account for the observed results (see below, eq 1). After the initial acylation to generate intermediates **46** and **37**, α,α-disubstituted β-ketoester **37** could be susceptible to ring opening under the reaction conditions, potentially leading to irreversible formation of cyclopropane **34**. In contrast, deprotonation of β-ketoester **46** under the reaction conditions could discourage the retro-Dieckmann process, preserving the lactone ring system **53**. Experiments conducted on a related ring system (eq 2) confirm the retro-Dieckmann type of bond cleavage in presence of NaOEt or NaH (see Supporting Information). Although the reaction analogous to the transformation of **37** to **34** was not observed in the model system, we cannot rule out the possibility that the reaction does occur in the merrilactone ring system. The authors thank Professor David Hart (The Ohio State University) and Professor Michael Harmata (The University of Missouri-Columbia) for suggesting this reaction mechanism to explain the contrasting results of the acylation reactions of **37** and **46**.



(61) Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, *55*, 202.

Birman, alcohol **51** was smoothly converted into merrilactone A (**1**) in 68% yield. The spectroscopic data of both the intermediate epoxide and the final product **1** were identical to those reported in literature for (±)-merrilactone A.

Conclusion

An efficient stereoselective total synthesis of (±)-merrilactone A was achieved via the newly developed catalytic Nazarov cyclization of silyloxyfurans. The primary roadblock in early efforts was in the construction of lactone ring D: undesired cyclopropanation formation predominating during all attempts to effect intramolecular acylation of tetrasubstituted derivatives derived from Nazarov product **23i**. This difficulty was finally overcome when derivatives of trisubstituted Nazarov product **23j** were used instead of the tetrasubstituted derivatives **23i**. During the synthetic studies, an interesting intramolecular Claisen condensation of a silyloxyfuran was observed, and Lewis acidic silicon species were implicated as participants in the catalytic cyclization reactions. This total synthesis of (±)-merrilactone A demonstrates that catalytic Nazarov cyclization methodology can be efficiently applied to problems in natural product synthesis. In particular, the silyloxyfuran cyclizations developed represent an unusual version of the Nazarov cyclization that should find additional applications in organic synthesis.

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Supporting Information Available: Experimental procedure, characterization data, X-ray crystal structure coordinates and files for compounds **28** and **41** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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