

# 1996 Merck Frosst Award Lecture

## Synthetic adventures along a Rocky Mountain road<sup>1</sup>

**Brian A. Keay, Shawn P. Maddaford, Walter A. Cristofoli, Neil G. Andersen, Marco S. Passafaro, Noel S. Wilson, and James A. Nieman**

**Abstract:** This paper describes the chemistry presented during the Merck Frosst Centre for Therapeutic Research Lecture Award given at the 79th Chemistry in Canada Conference held in St. John's, Newfoundland in June 1996. The first section describes the synthesis of (+)-xestoquinone using an asymmetric palladium-catalyzed polyene cyclization as the key step that creates the C and D rings and the stereogenic centre (68% ee) in one step. Extensions of the work involving an in situ Suzuki reaction are presented. The synthesis of  $C_2$ -symmetric biaryls and the synthesis of a recently isolated binaphthyl natural product is described using this new method. A new one-pot desilylation–oxidation procedure of silyl ethers is described in detail for the preparation of aldehydes and ketones directly without the need for the isolation of the alcohol intermediate. Finally, a highly diastereoselective (>97%) Diels–Alder reaction is presented using (+)-*cis,cis*-spiro[4.4]nonane-1,6-diol as a new chiral auxiliary. One of the alcohols is attached to a pivalate, the other to an acrylate, and the Diels–Alder reaction with cyclopentadiene provides only one adduct (by <sup>1</sup>H NMR and HPLC) with the *endo* stereochemistry.

**Key words:** (+)-xestoquinone, asymmetric palladium-catalyzed polyene cyclization, in situ Suzuki reaction, desilylation–oxidation reaction, spirodiols, chiral auxiliaries.

**Résumé :** Cette publication décrit la chimie présentée lors de la remise du prix du Centre Merck–Frosst pour la recherche thérapeutique, lors de la 79<sup>e</sup> Conférence de chimie au Canada, tenue à St-Jean, Terre-Neuve, en juin 1996. La première section décrit la synthèse de la (+)-xestiquinone impliquant, comme étape clé, une cyclisation de polyène catalysée par du palladium asymétrique conduisant, en une étape, à la création des cycles C et D et du centre stéréogène (68% ee). On présente des extensions de ce travail impliquant une réaction de Suzuki in situ. Faisant appel à cette méthode, on a réalisé la synthèse de biaryles de symétrie  $C_2$  et d'un produit naturel de la série des binaphtyles qui a été isolé récemment. On décrit en détail une procédure unipot de désilylation–oxydation des éthers silylés permettant de préparer directement des aldéhydes et des cétones sans avoir à isoler l'alcool intermédiaire. Enfin, on présente une réaction de Diels–Alder fortement diastéréosélective (>97%) faisant appel au (+)-*cis,cis*-spiro[4,4]nonane-1,6-diol comme nouvel auxiliaire chiral. On a attaché l'un des groupes hydroxyles à un pivalate et l'autre à un acrylate, et la réaction de Diels–Alder avec le cyclopentadiène ne fournit qu'un seul adduit (RMN du <sup>1</sup>H et CLHP) dont la stéréochimie est *endo*.

**Mots clés :** (+)-xestoquinone, cyclisation de polyène catalysée par du palladium asymétrique, réaction de Suzuki in situ, réaction de désilylation–oxydation, spirodiols, auxiliaires chiraux.

[Traduit par la rédaction]

### Introduction

The title of the talk was chosen for two reasons. First, it was important to incorporate the fact that most of the work in this presentation was performed in Calgary. This was done by incorporating “Rocky Mountain” into the title since Calgary is very close (~90 km) to the Rocky Mountains. Second, if one

word is removed from the title, its context changes dramatically. Removing the word “Mountain” provides the title, “Synthetic Adventures Along a Rocky Road.” This title is a reminder that ideas, and what are believed to be the best thought-out plans, do not always proceed<sup>3</sup> in a smooth and orderly manner. Many unforeseen obstacles are encountered during the course of academic research. It is the perseverance, hard work, and dedication of excellent graduate students and post-doctoral Fellows that result in solutions to unforeseen problems and oftentimes lead to new discoveries. It is to past<sup>4</sup>

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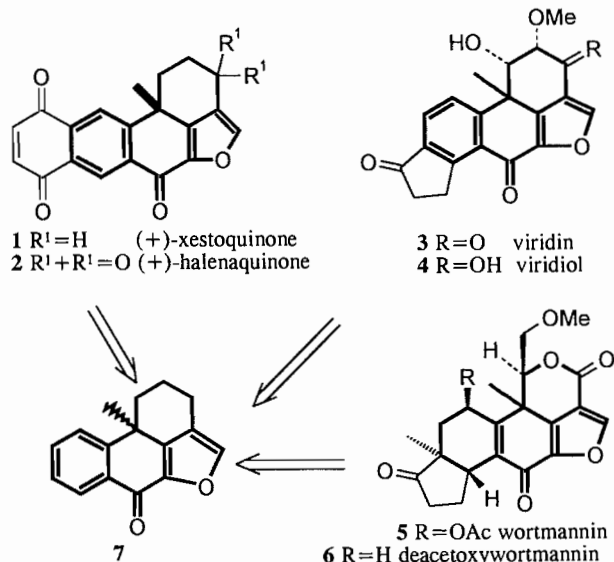
<sup>1</sup> This paper is an invited review article based on the Merck Frosst Centre for Therapeutic Research Award Lecture presented by Professor Keay at the 79th Annual Conference of the Canadian Society for Chemistry, St. John's, Newfoundland, June 1996.

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<sup>3</sup> It has been my experience that most of the ideas proposed to date have developed problems at some point along the way. Investigations almost *never* proceed as planned. Many new discoveries and some very interesting chemistry have been found as a result of these obstacles, and some of the chemistry that has developed from these pitfalls is presented in this paper.

<sup>4</sup> I did not present work done by the following past members of my group: Ted J. Bures, Patrick G. Spinazzé, Jean-Louis J. Bontront, Giovanna Beese, Dr. Christine Rogers, Dr. Simon Woo, and Dr. Shuyuan Yu.

Scheme 1.



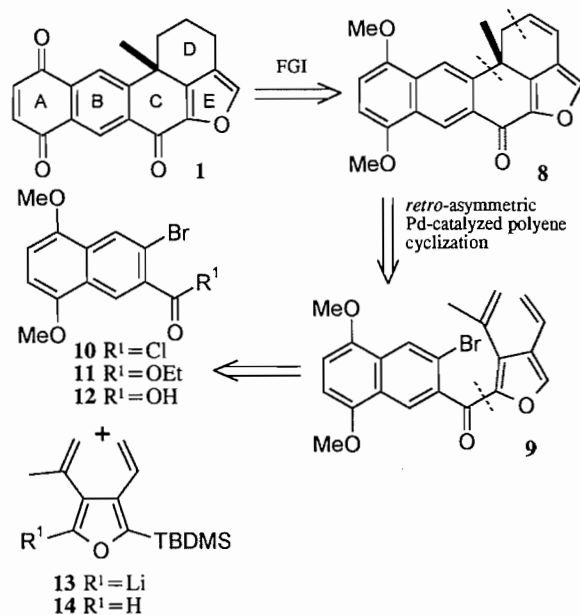
and present members<sup>5</sup> of my group that I dedicate this talk, since I would not be presenting this work if not for the excellent chemistry discovered and performed by these people. For this I thank them.

The paper will be divided into four parts. First, the synthesis of (+)-xestoquinone will be discussed, in which an asymmetric palladium-catalyzed polyene cyclization was used to create rings C and D and the stereogenic centre in one step. Second, extensions of our modified in situ Suzuki reaction in which the Shapiro and Suzuki reactions are combined into a one-pot procedure will be illustrated and a new method for the preparation of C<sub>2</sub>-symmetric biaryls is described along with the synthesis of a C<sub>2</sub>-symmetric binaphthalene natural product. Third, a new one-pot procedure that combines a desilylation-oxidation sequence using catalytic quantities of PdCl<sub>2</sub> will be presented in detail. Finally, the use of (+)- and (-)-*cis,cis*-spiro[4.4]nonane-1,6-diol as new chiral auxiliaries for the Diels-Alder reaction, in which one of the alcohols is substituted with a pivalate and the other with an acrylate, will be described.

### Synthesis of (+)-xestoquinone

Xestoquinone **1** (1) and halenaquinone **2** (2) were isolated from Pacific sponges and shown to possess a unique pentacyclic carbon framework (Scheme 1). Both **1** and **2** (especially **2**) are irreversible inhibitors of oncogenic protein tyrosine kinase pp60<sup>v-src</sup> and the human epidermal growth factor kinase (EGF) (3). Xestoquinone also has a positive inotropic effect on cardiac muscle that leads to it being a potent cardiotoxic agent (4). Four of the rings common to both **1** and **2** are found in the Viridin class of natural products **3-6** (5) as illustrated in Scheme 1. We envisioned that if a short asymmetric route to tetracycle **7** could be developed, then the approach could be applicable towards the preparation of natural products **1-6**. We also chose (+)-xestoquinone as our initial target as it contained

Scheme 2.



the least number of functional groups and had not been synthesized asymmetrically, although Harada reported the diastereoselective synthesis of **1** starting with optically pure Wieland-Miescher ketone (6).<sup>6</sup>

Space limitations do not permit the description of the many unsuccessful approaches towards the synthesis of **1** (11). The retrosynthesis that was finally successful is illustrated in Scheme 2 (12). Functional group interconversion of **1** provides **8**, which after a retro-palladium-catalyzed polyene cyclization gives **9**. Disconnection between the furan ring and ketone in **9** provides tetrasubstituted naphthoyl chloride **10** and lithio-furan **13**. The advantages of this approach are (i) that rings C and D are introduced in a single step with concurrent formation of the single stereogenic centre; (ii) that the polyene cyclization can be performed in the presence of a chiral ligand such as (+)-BINAP so that the synthesis is asymmetric; and (iii) that the synthesis is convergent, requiring the preparation and coupling of naphthalene **10** and furan **13**. Other asymmetric polyene cyclizations sequences (13) and Heck reactions (14) have been reported; however, the former has not been applied to the enantioselective synthesis of a natural product (12).

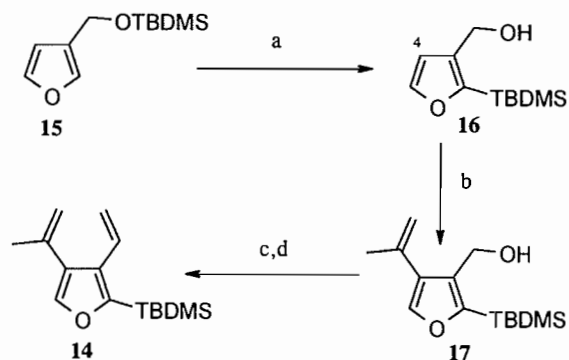
Naphthoyl chloride **10** was prepared from the known ester **11** (15) in two steps by hydrolysis of ester **11** (K<sub>2</sub>CO<sub>3</sub>, refluxing methanol, 95%) followed by treatment of acid **12** with oxalyl chloride in methylene chloride containing a drop of DMF (>99%) (Scheme 2).

Furan **14** was prepared using some chemistry we discovered in 1988 (16). Furan rings tend to lithiate at the C-2 position and (or) at the C-5 position if the C-2 position is substituted. Thus, the preparation of 3,4-disubstituted furan rings is difficult. We reported that 2-silylated-3-hydroxymethylfuran

<sup>5</sup> I did not present work done by the following current members of my group: Dr. Ian R. Hunt and Bryon E. Carpenter.

<sup>6</sup> Kanematsu et al. have reported a formal synthesis of (±)-**1** (7). Harada et al. (8), Shibasaki and co-workers (9) have reported syntheses of **2** and Rodrigo and co-workers (10) have reported the synthesis of **1** and **2**.

Scheme 3.



**Reagents:** (a) *n*-BuLi, THF, HMPA, 0°C–rt, 12 h (87%); (b) 2.2 equiv. *n*-BuLi, DME, 0°C; then B(O<sup>i</sup>Pr)<sub>3</sub>, 1 h, 0°C; then Pd(PPh<sub>3</sub>)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, 2-bromopropene, reflux, 13 h (95%); (c) PDC, CH<sub>2</sub>Cl<sub>2</sub>, rt (85%); (d) Ph<sub>3</sub>PCH<sub>2</sub>, THF, 1 h, reflux (95%).

when treated with 2.2 equiv. of *n*-BuLi results in exclusive lithiation at the C-4 position (16). We used this chemistry to prepare furan **14** (Scheme 3). Treatment of **15** with 1.1 equiv. of *n*-BuLi in THF containing 1 equiv. of HMPA resulted in the formation of furan **16** (87%) via an intramolecular 1,4 O → C silyl migration (17).

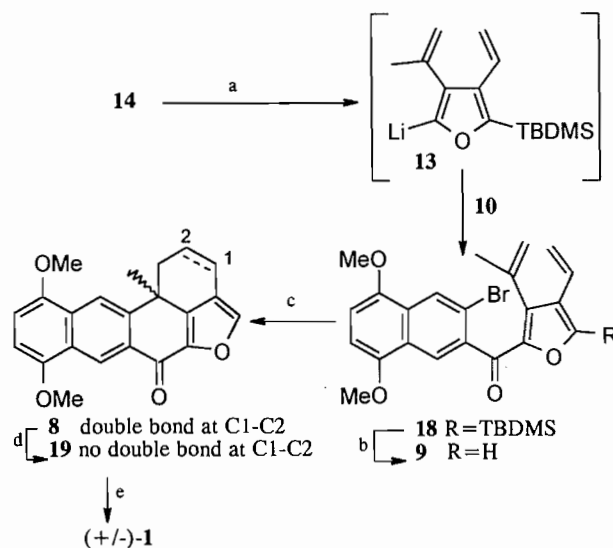
We investigated using the Stille (18) and Suzuki (19) reactions to introduce the 2-propenyl group through a palladium coupling with the corresponding C-4 stannane and boronic acid, respectively; however, the Stille coupling gave very poor yields (20) and the C-4 boronic acid species of **16** could not be isolated by quenching the C-4 anion with trimethylborate (21). An in situ variant of the Suzuki reaction was developed (12, 21, 22) in which the C-4 anion of **16** was quenched with triisopropylborate and, after 1 h, immediately treated with Pd(PPh<sub>3</sub>)<sub>4</sub> (3 mol%), 2 M Na<sub>2</sub>CO<sub>3</sub>, and 2-bromopropene at reflux for 13 h. Furan **17** was obtained in 95% yield. The required trisubstituted furan **14** was prepared by PDC oxidation of **17** (85%) followed by a standard Wittig reaction (95%).

Furan **14** was lithiated at C-5 by treatment with 1.5 equiv. of *n*-BuLi in the presence of 1.2 equiv. HMPA (THF, -78°C) to form **13**, which was immediately reacted with freshly distilled naphthoyl chloride **10**. Furan **18** was isolated in 79% yield (Scheme 4). Compound **18** is the precursor for a palladium-catalyzed polyene cyclization. Although we attempted to perform the cyclization reaction on **18**, a mixture of products was always obtained. Removal of the silyl group prior to attempting the polyene cyclization alleviated the formation of complex mixtures (vide infra) (12, 13a). The silyl group in **18** was removed with *n*-Bu<sub>4</sub>NF (THF, 0°C), providing **9** in 95% yield.

We initially decided to prepare (±)-xestoquinone **1** in order to demonstrate the viability of the synthetic strategy. Refluxing a mixture of **9** with Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd<sub>2</sub>(dba)<sub>3</sub> (10 mol%) in NMP containing Et<sub>3</sub>N provided pentacycle **8** in 82% yield. Compound **8** was converted into (±)-xestoquinone **1** by catalytic hydrogenation (H<sub>2</sub>, Pd/C, 1 atm (101.3 kPa), 4 h, 99%) to form **19** followed by a ceric ammonium nitrate oxidation (CH<sub>3</sub>CN/H<sub>2</sub>O, 0°C, 5 min) according to the procedure reported by Harada et al. (6) (Scheme 4).

With a successful route towards (±)-xestoquinone in hand, we turned our attention to attempting an asymmetric

Scheme 4.



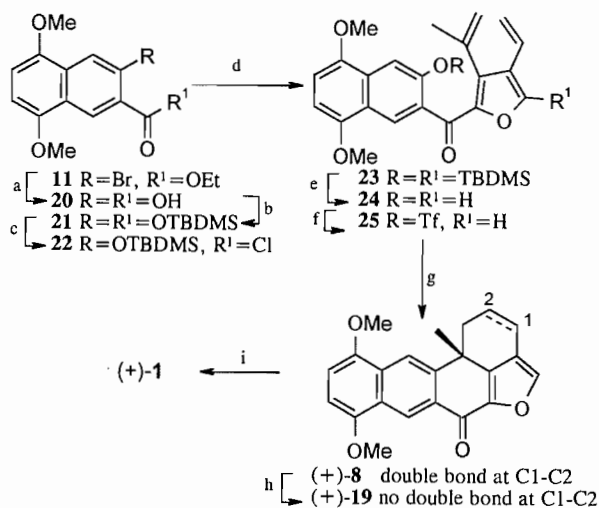
**Reagents:** (a) *n*-BuLi (1.5 equiv.), HMPA (1.5 equiv.), THF, 0°C; then add **10** (79%); (b) *n*-Bu<sub>4</sub>NF, THF, 0°C (95%); (c) Pd(PPh<sub>3</sub>)<sub>4</sub>, NMP, Et<sub>3</sub>N, (82%); (d) H<sub>2</sub> (1 atm), 5% Pd/C, EtOH, rt (99%); (e) CAN, CH<sub>3</sub>CN, H<sub>2</sub>O, 5 min.

palladium-catalyzed polyene cyclization. Treatment of **9** with a variety of chiral palladium catalysts provided **8** with very poor enantiomeric excesses (ee's) (Pd((*R*)-BINAP)<sub>2</sub>/Et<sub>3</sub>N (5% ee), Pd((*R*)-BINAP)<sub>2</sub>/PMP (13% ee), or Pd((2*R*,3*R*)-chiraphos)<sub>2</sub>/PMP (7% ee)) that could not be improved by the addition of silver salts (23). In hopes of increasing the %ee of the polyene cyclization we investigated the use of a triflate instead of a bromine atom in **9**, since it has been reported that triflates provide much higher ee's than bromides or iodides in the Heck reaction due to the increased liability of the Pd—OTf bond when compared to Pd—Br and Pd—I bonds (14b).

The bromine atom in **11** (Scheme 5) was changed into a hydroxy group and subsequently converted into a naphthyl triflate prior to the polyene cyclization. Halogen-metal exchange of the bromine atom in **11** with *n*-BuLi (-95°C, THF) followed by the immediate addition of trimethylborate and a basic H<sub>2</sub>O<sub>2</sub> work-up provided acid **20** (87%). Bis-silylation of **20** with TBDMSOTf (2 equiv.) gave **21** (79%), which was converted into naphthoyl chloride **22** by treatment with oxalyl chloride in refluxing hexanes containing a drop of DMF (99%). Acid chloride **22** was added slowly to a solution of anion **13**, which was generated by treatment of **14** with *s*-BuLi (THF, -78°C) to provide ketone **23** after work-up (42% from **20**). Removal of both silyl groups with *n*-Bu<sub>4</sub>NF (THF, 0°C) provided **24**, which when treated with NaH in DMF followed by the addition of PhNTf<sub>2</sub> gave triflate **25**.

Triflate **25** was used immediately in the asymmetric polyene cyclization, since it was found to be very sensitive to air and moisture. Treatment of **25** using Pd((*S*)-BINAP)<sub>2</sub> gave pentacycle (+)-**8** with 68% ee (82% from **24**). Compound (+)-**8** was also shown to have the correct absolute stereochemistry required for the preparation of (+)-**1** (12). Finally, (+)-xestoquinone (**1**) (68% ee) was synthesized by catalytic hydrogenation of (+)-**8** to provide (+)-**19** (100%) followed by a ceric

Scheme 5.



**Reagents:** (a) *n*-BuLi, THF,  $-95^{\circ}\text{C}$ ; then  $(\text{MeO})_3\text{B}$ ; then add  $\text{H}_2\text{O}_2$ , NaOH; then 10% HCl (87%); (b) TBDMSOTf,  $\text{Et}_3\text{N}$  (79%); (c) oxalyl chloride, 1 drop of DMF, hexanes (99%); (d) **13** generated from *s*-BuLi/THF (42% from **20**); (e) *n*-Bu<sub>4</sub>NF, THF,  $0^{\circ}\text{C}$  (95%); (f) NaH, DMF, rt, PhNTf<sub>2</sub> and used immediately; (g) Pd<sub>2</sub>(dba)<sub>3</sub>(2.5 mol%), *S*-BINAP (10 mol%), PMP, toluene, reflux, 22 h (82% from **24**; 68% ee); (h) H<sub>2</sub> (1 atm), 5% Pd/C, EtOH, rt (95%); (i) CAN, CH<sub>3</sub>CN, H<sub>2</sub>O, 5 min.

ammonium nitrate oxidation (Scheme 5). The <sup>1</sup>H NMR and CD spectra of synthetic (+)-xestoquinone were identical with those provided to us by Prof. Harada (6).

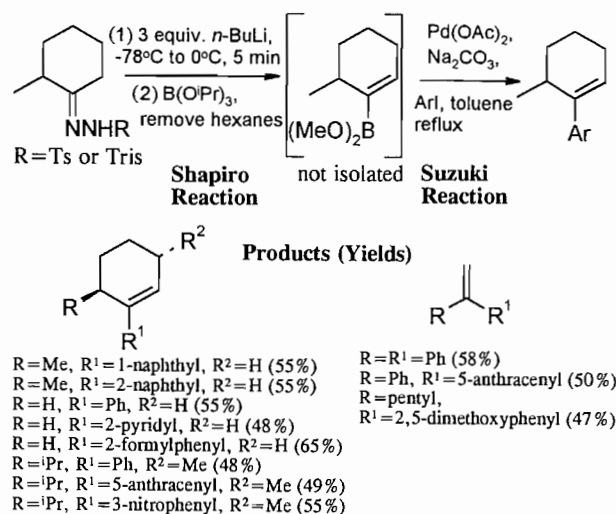
Thus, we have developed a short convergent asymmetric route to (+)-xestoquinone, which represents the first synthesis of a natural product incorporating an asymmetric palladium-catalyzed polyene cyclization. Work is continuing on: (i) improving the %ee of the polyene cyclization, (ii) developing a rationale to explain the observed absolute stereochemistry of the cyclization; and (iii) applying this reaction towards the synthesis of other natural products (i.e., **2-6**, Scheme 1).

#### Further extensions of the in situ Suzuki reaction

As mentioned above, compound **17** was prepared by developing an in situ variation of the Suzuki reaction (21, 22). We have recently expanded the scope and limitations of this reaction by showing that: (i) the Shapiro (24) and Suzuki (19) reactions can be combined into a one-pot reaction sequence (25); and (ii) C<sub>2</sub>-symmetric biaryls can be prepared in one step starting with a haloarene (26). These new applications are summarized below.

It is well known that when tosyl- or trisylhydrazones are treated with excess *n*-BuLi (>3 equiv.), a vinyl anion develops that can be trapped with a variety of electrophiles (Scheme 6) (24). We investigated whether the anion could be trapped with trimethylborate and subsequently used in a Suzuki reaction without the need for isolation of the vinyl boronic acid. Although we were successful in combining the reactions in one pot, unfortunately a change of solvent was required for the Suzuki reaction. The Shapiro reaction was performed in a mixture of hexanes and TMEDA but the Suzuki reaction would not proceed unless the hexanes were removed and replaced with toluene. Similarly, the Shapiro reaction did not proceed in

Scheme 6.

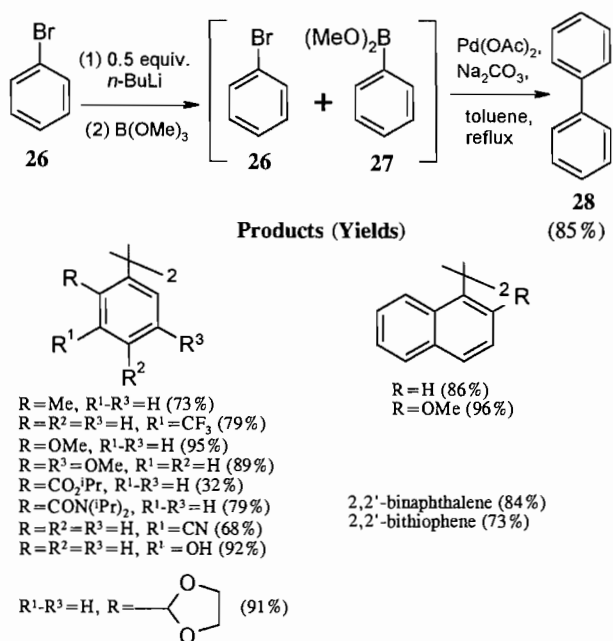


toluene. Nevertheless, the reaction can be performed in one pot and appears to be quite general. Thus, the anion that forms from the Shapiro reaction is quenched with B(OMe)<sub>3</sub>, and after 1 h the hexanes are removed in vacuo. The addition of toluene, Na<sub>2</sub>CO<sub>3</sub>, Pd(OAc)<sub>2</sub> (5 mol%), PPh<sub>3</sub> (10 mol%), the aryl or vinyl iodide (or bromide), and reflux of the resulting mixture affords the desired products in yields ranging from 47 to 65% (Scheme 6) (25). It was determined that the yields are limited by the Shapiro reaction since isolation of the vinyl boronic acids and subsequent treatment under Suzuki conditions provided the coupled products in excellent yield. We are currently applying this combined reaction sequence towards the preparation of monoterpenylmagnolol (27).

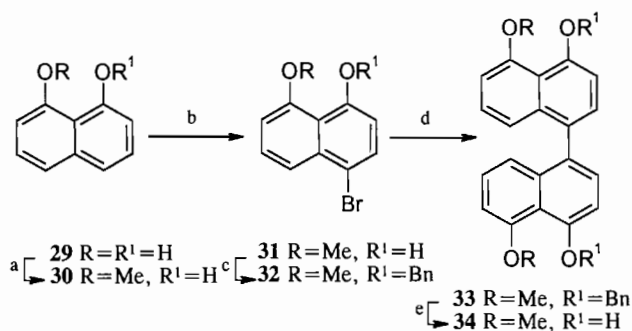
The second extension of the in situ Suzuki reaction involves the formation of C<sub>2</sub>-symmetric biaryls starting only from the arylhalide. In 1994, we reported on the scope and limitations of the in situ Suzuki reaction (22) and showed that iodobenzene could be completely halogen-metal exchanged with *t*-BuLi and the resulting anion quenched with B(OMe)<sub>3</sub>. A second aryl- or vinylhalide was added along with a palladium catalyst, which after refluxing afforded the coupled product in good to excellent yields. In this procedure, the two aryl components could be different. However, if a C<sub>2</sub>-symmetric biaryl was required, we reasoned that the above procedure could be modified slightly so that the second equivalent of arylhalide would not have to be added to the solution after the B(OMe)<sub>3</sub> was added (26). The modification was to initially add only 0.5 equiv. of *n*-BuLi so that only 50% of the arylhalide would undergo a halogen-metal exchange. The addition of (MeO)<sub>3</sub>B would quench the resulting anion and leave a 50/50 mixture of arylboronate and arylhalide (Scheme 7, **26** and **27**), that should undergo a Suzuki coupling if a palladium catalyst is introduced into the flask. This modification was realized when bromobenzene **26**, when treated as above, provided biphenyl **28** in 85% yield when toluene, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Ba(OH)<sub>2</sub> were added to the solution and subsequently refluxed (Scheme 7) (26). The procedure is quite general and a variety of C<sub>2</sub>-symmetric biaryl compounds have been prepared in moderate to good yields (Scheme 7).

This method has also been used to prepare 4,4'-

Scheme 7.



Scheme 8.

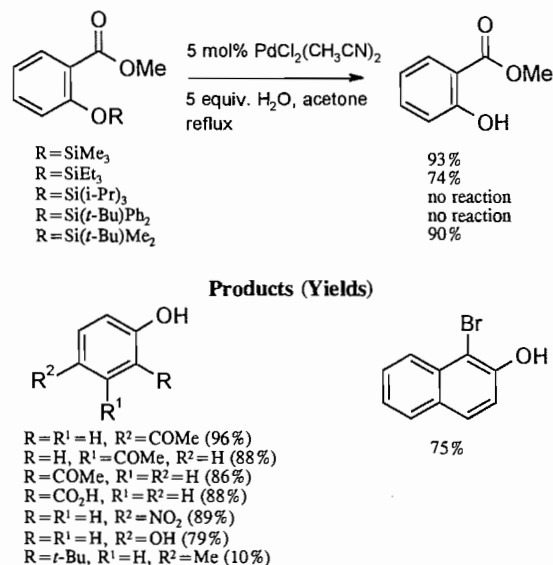


**Reagents:** (a) 1 equiv. NaH, DMF, 5 equiv. MeI (95%); (b) NaH,  $\text{CCl}_4$ , 1 equiv.  $\text{Br}_2$  (60%); (c) NaH, DMF, BnBr (100%); (d) 0.5 equiv. *n*-BuLi, THF,  $-78^\circ\text{C}$ ; then  $\text{B}(\text{OMe})_3$ , rt, 12 h; then toluene, EtOH,  $\text{H}_2\text{O}$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{Pd}(\text{PPh}_3)_4$ , reflux, 12 h (72%); (e)  $\text{H}_2$ , Pd/C, EtOH/ $\text{CH}_2\text{Cl}_2$  (100%).

dihydroxy-5,5'-dimethoxy-1,1'-binaphthalene **34**, which has been isolated from the fungus (Ascomycetes) *Daldinia concentrica* (**28**). Our synthesis began with 1,8-naphthalenediol **29**, which was prepared from 1,8-naphthosultone (**29**). Diol **29** was converted into **34** in five steps with an overall yield of 41% (Scheme 8). Monomethylation of **29** produced **30**, which underwent a regioselective bromination *para* to the hydroxyl group, giving **31**. Unfortunately, the synthesis was extended by two steps because the hydroxy group in **31** had to be protected. Halogen-metal exchange of **31** by treatment with *n*-butyllithium provided an excellent yield of 8-methoxy-1-naphthol (**30**). Protection of the free hydroxyl group with a benzyl group alleviated this problem. Binaphthalene **34** was prepared by an in situ palladium coupling of **32** (to give **33**) followed by removal of the benzyl protecting groups by hydrogenolysis.

We have shown that the in situ variant of the Suzuki reaction is a general viable process for the preparation of a variety

Scheme 9.



of compounds. It was used in the preparation of furan **14**, which was a key intermediate in the syntheses of (+)-xestoquinone **1** and binaphthalene **34**. Further extensions of this reaction are currently underway.

#### Development of a one-pot desilylation-oxidation of silyl ethers using catalytic amounts of $\text{PdCl}_2$

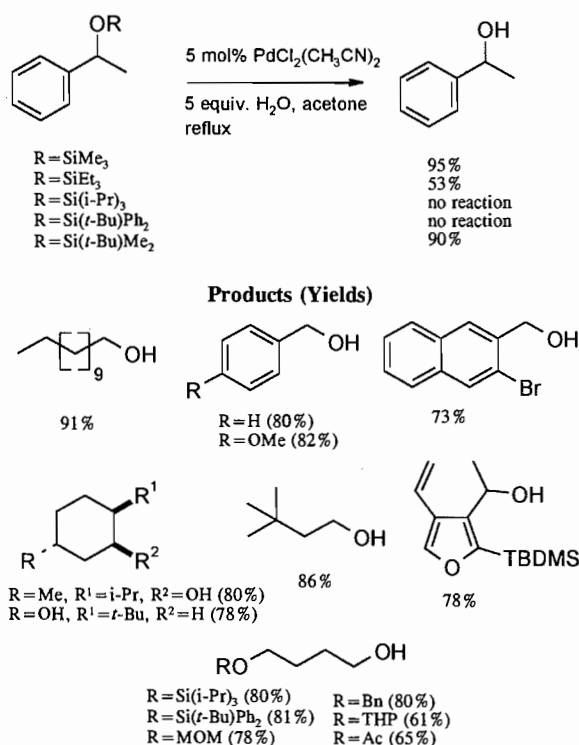
During some work on the palladium-catalyzed polyene cyclization towards xestoquinone, we noticed that a phenol protected as its *tert*-butyldimethylsilyl ether was cleaved in the presence of  $\text{Pd}(\text{OAc})_2$ . Since we could not find any reports on the removal of phenolic silyl ethers with palladium catalysts, we investigated this reaction further (31–35).

A variety of phenolic *tert*-butyldimethylsilyl ethers were cleaved to their respective phenols by treatment with 1–5 mol%  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  in refluxing reagent grade acetone containing 5 equiv. of water (Scheme 9) (36).<sup>7</sup> Products were formed in yields ranging from 10 to 96%. Both the water and palladium catalyst were necessary for a successful reaction. Hindered silyl ethers were removed very slowly (see the last example) and a variety of functional groups were tolerated during this reaction (halides, esters, nitriles, nitro, aldehydes, and ketones). The reaction was not limited to the *tert*-butyldimethylsilyl ether; trimethyl- and triethylsilyl ethers were desilylated, while triisopropyl- and *tert*-butyldiphenylsilyl ethers were inert under these reaction conditions. Since phenolic silyl ethers were removed with catalytic amounts of  $\text{PdCl}_2$  we looked at whether aliphatic silyl ethers could be desilylated under similar reaction conditions.

Treatment of a variety of aliphatic *tert*-butyldimethylsilyl ethers with 5 mol%  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  in acetone containing

<sup>7</sup> We have recently shown that trimethyl-, triethyl-, *tert*-butyldimethyl-, triisopropyl-, and *tert*-butyldiphenylsilyl phenolic ethers can be removed by refluxing the silyl ether in ethanol containing 1.1 equiv. of  $\text{K}_2\text{CO}_3$ . Aliphatic silyl ethers were not removed under these reaction conditions. See ref. 37 for further details.

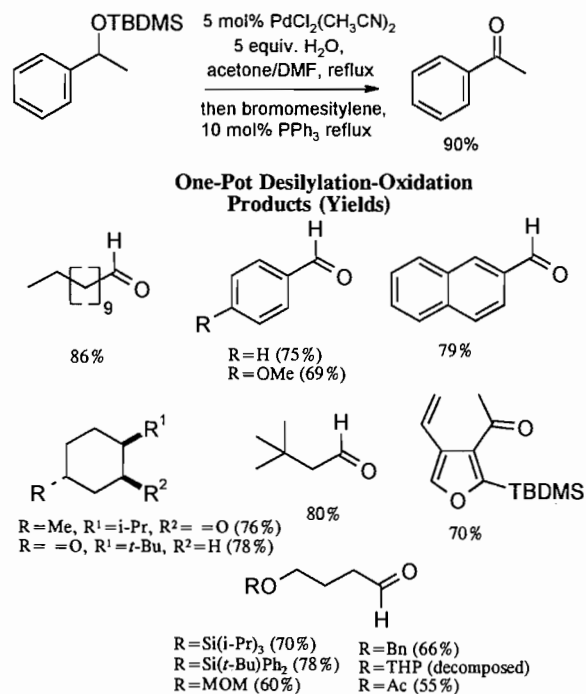
Scheme 10.



5 equiv. of water provided desilylated materials in yields ranging from 73 to 91% (Scheme 10) (38).<sup>8</sup> The reaction conditions also desilylated trimethylsilyl ethers; however, triisopropyl- and *tert*-butyldiphenyl-silyl ethers did not react under these conditions. Triethylsilyl ethers were somewhat capricious and approximately 50% desilylation was all that could be obtained under the best of conditions. The *tert*-butyldimethylsilyl group could also be removed selectively in the presence of triisopropylsilyl, *tert*-butyldiphenylsilyl, methoxymethyl, benzyl, tetrahydropyranyl, and acetate protecting groups (Scheme 10). The reaction is quite general and a number of functional groups were tolerated. In addition, a Si—O bond could be selectively cleaved in the presence of a Si—C bond (see the furan example).

Tamaru et al. reported in 1979 that alcohols could be oxidized to aldehydes and ketones with catalytic amounts of palladium acetate and a stoichiometric amount of 2-bromomesitylene in dry DMF (40). Since desilylations are possible using PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, we investigated whether the desilylation and oxidation reactions could be combined into a one-pot sequence using catalytic amounts of a palladium catalyst (38). We have successfully combined the two reactions into a one-pot sequence using a 1:1 mixture of acetone:DMF as the solvent with 5 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>. The mixed solvent system is essential for the success of the combined reactions since the desilylation reaction would not proceed in wet (or dry) DMF and the oxidation would not proceed in wet (or

Scheme 11.



dry) acetone. At this time we do not understand why the mixed solvent system works while the individual solvents do not work on opposite reactions, but we are still investigating this intriguing observation.

The reaction is performed by mixing the silyl ether with the palladium catalyst in an acetone–DMF mixture containing 5 equivalents of water. The mixture is heated to reflux and, once TLC or GC indicates the silyl group has been removed, 2-bromomesitylene (oxidizing agent), PPh<sub>3</sub> (10 mol%), and K<sub>2</sub>CO<sub>3</sub> are added and refluxed until the reaction is complete. Aldehydes and ketones are formed in yields ranging from 69 to 90% depending on the substrate (Scheme 11). Aldehydes are not overoxidized to the carboxylic acid, and even benzaldehyde was isolated in 75% yield. The reaction is not general and we have found three limitations so far: (i) aryl bromides and iodides are dehalogenated during the procedure. Thus, 3-bromo-2-(*tert*-butyldimethylsilyl)oxymethyl-naphthalene provided a 79% yield of 2-naphthaldehyde; (ii) *O*-(*tert*-butyldimethylsilyl)cinnaminol provided cinnamaldehyde in only 10% yield. Allylic alcohols appear to require stoichiometric amounts of the palladium species; finally (iii) a THP and acetate protecting group were not tolerated very well during this one-pot sequence (Scheme 11). Nevertheless, many examples provided aldehydes and ketones in good to excellent yield and we highly recommend this procedure over the two-step process that is normally used.

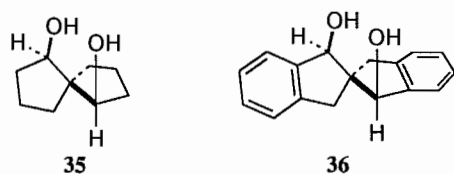
#### *cis,cis*-Spiro[4.4]nonane-1,6-diol: new chiral auxiliaries for the Diels–Alder reaction

For the past 4 years we have been investigating the synthesis and use of C<sub>2</sub>-symmetric spirodiols as auxiliaries in various organic transformations (41–44). To date, we have concentrated our efforts on the preparation of *cis,cis*-spiro[4.4]nonane-1,6-diol **35** and *cis,cis*-2,2'-spirobiindane-1,1'-diol **36** (Scheme 12). At the time we started our investigation,

<sup>8</sup> Lipshutz et al. reported the desilylation of a *tert*-butyldimethylsilyl ether as a side reaction when an acetal was being cleaved using PdCl<sub>2</sub>. See ref. 39.



## Scheme 12.



there were no reports on the use of **35** and **36** as chiral auxiliaries; however, in 1992 Kumar and co-workers reported that **36** could be used with lithium aluminium hydride for the asymmetric reduction of aromatic ketones (45). Attempts to repeat these results by us, and later by Seebach's group (46), failed to reproduce the results reported by Kumar. We therefore carried on with our investigation. The synthesis and resolution of ( $\pm$ )-**35** (41) and ( $\pm$ )-**36** (43) and the confirmation of the absolute stereochemistry of **35** using a combination of an X-ray crystal structure, VCD spectra, and ab initio calculations have been reported (42) and will not be presented in this article. Instead, the application of (+)- and (–)-**35** as chiral auxiliaries in the Diels–Alder reaction will be discussed in detail. While other diols have been used as chiral auxiliaries in the Diels–Alder reaction (47), to our knowledge this is the first time **35** has been used as such (48).

Although we have used (+)-**35** as a Lewis acid bound chiral auxiliary in the Diels–Alder reaction (Ti) (49), cyclopropanation reaction (Zn) (50), Grignard addition to aryl ketones (Mg) (51), and hydrocyanation reaction (Ti) (52), the enantiomeric excesses (ee's) of the products were never any better than those reported with other diols (48). We then looked at using **35** as a substrate-bound chiral auxiliary. When **35** was used as the alcohol component to prepare acetals and ketals from aldehydes and ketones and used in a variety of diastereotopic reactions (i.e., *ortho*-lithiation of arylacetals and condensation of the anion with aldehydes (53), diastereoselective Ullmann (54) and Suzuki couplings (19, 22) with *ortho*-bromoarylacets, and cyclopropanation of unsaturated acetals (55)), the diastereomeric excesses (de's) were similar to those reported with other diols (48). The best result obtained with **35** was in the Diels–Alder reaction when a dienophile was attached to one alcohol and a blocking group to the other.

Initially we focused our attention on determining which Lewis acid would provide the highest yield and greatest amount of *endo* isomer in the Diels–Alder reaction between an acrylate and cyclopentadiene. The blocking group chosen was the 2-naphthoate group as Maitra and Mathivanan have reported success with this group when attached to a steroidal backbone (47*d* and *e*). Some selected results are illustrated in Table 1 (entries 1–6). The best result was when **37** (R = 2-Np) was treated at  $-85^{\circ}\text{C}$  with 2 equiv. of boron trichloride containing freshly distilled cyclopentadiene. Adduct **38** (R = 2-Np) was formed in 100% yield with 96% *endo* stereochemistry and had a de of 75%.

A variety of blocking groups were used to replace the 2-naphthyl group and the Diels–Alder reaction was attempted using  $\text{BCl}_3$ . Changing the blocking group to a 1-naphthyl group did not noticeably change the results, but an increase in the de from 75% to 88% was observed when a phenyl group was used in **37**. Replacing the phenyl group with an electron-deficient (R = *p*- $\text{NO}_2\text{Ph}$ ) and electron-rich (R = MeOPh)

Table 1. Results for the Diels–Alder reaction of **37**.

R	Equiv. of Lewis acid	Lewis acid	<i>endo</i> <sup>a,b</sup> (%)	%de <sup>b</sup> (%ee)	<b>38</b> <sup>b</sup> (%)
2-Np	—	—	84	7	100 <sup>c</sup>
2-Np	1.1	$\text{TiCl}_4$	97	54	6
2-Np	1.1	$\text{SnCl}_4$	95	80	15
2-Np	2.1	$\text{SbCl}_5$	94	53	74
2-Np	3	$\text{AlMeCl}_2$	97	59	100
2-Np	2	$\text{BCl}_3$	96	75	100
( <i>R</i> )-1-Np <sup>d</sup>	2	$\text{BCl}_3$	98	75 <sup>e</sup>	100
Ph	2	$\text{BCl}_3$	99	88 <sup>e</sup>	100
<i>p</i> - $\text{NO}_2\text{Ph}$	2	$\text{BCl}_3$	98	84 <sup>e</sup>	100
<i>p</i> -MeOPh	2	$\text{BCl}_3$	98	88 <sup>e</sup>	100
( <i>R</i> )-Ph <sup>d</sup>	2	$\text{BCl}_3$	99	88 <sup>e</sup> (89)	100
$\text{Ph}_2\text{CH}$	2	$\text{BCl}_3$	97 <sup>f</sup>	90 <sup>f</sup>	100 <sup>f</sup>
( <i>S</i> )- $\text{Me}_3\text{C}^d$	2	$\text{BCl}_3$	99	>97 <sup>e</sup> (97)	100

<sup>a</sup>The remainder was the *exo* isomer.

<sup>b</sup>*endo* Diastereomers, determined by HPLC using an ODS column with  $\text{MeOH}/\text{H}_2\text{O}$  (90:10), unless otherwise indicated.

<sup>c</sup>Cyclopentadiene was added to the reaction mixture at  $8^{\circ}\text{C}$  until the reaction was complete.

<sup>d</sup>The letter in parentheses refers to the absolute configuration of the *cis,cis*-diol used (i.e., R = 1*R*,5*R*,6*R*).

<sup>e</sup>Cyclopentadiene was precooled to  $-85^{\circ}\text{C}$  in  $\text{CH}_2\text{Cl}_2$  and transferred to the reaction by cannula addition.

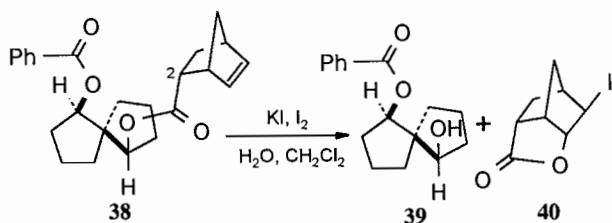
<sup>f</sup>Determined by  $^1\text{H}$  NMR spectroscopy.

aromatic ring did not noticeably change the %de, indicating stereoelectronic factors were not really important in this reaction. The steric size of the blocking group was increased by adding a diphenylbenzoate group to **37**, which resulted in a slight increase in the de to 90%. Following along the lines of increasing the steric bulk, a pivalate was attached to **37**. When the cyclopentadiene was precooled to  $-85^{\circ}\text{C}$  prior to its addition to a mixture of **37** (R =  $\text{CMe}_3$ ) and  $\text{BCl}_3$ , only one *endo* isomer was detected by HPLC and  $^1\text{H}$  NMR spectroscopy.

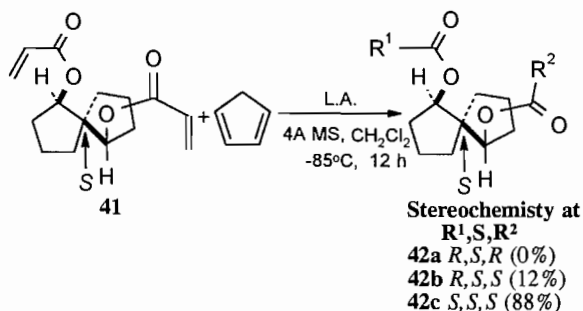
This result is remarkable when one considers all the possible conformations that **37** can adopt prior to the Diels–Alder reaction. Either one conformation is preferentially formed with **37** (R =  $\text{CMe}_3$ ) in the presence of 2 equiv. of  $\text{BCl}_3$ , thereby exposing only one face of the dienophile, or more than one conformation exists; but within each, the same face of the dienophile is exposed so that only one *endo* isomer is formed. Whatever the case, the result indicates that the spirononane **35** is a useful auxiliary in the Diels–Alder reaction.

The absolute stereochemistry of the bicyclo component of **38** was determined by treatment of **38** with  $\text{I}_2$ –KI in  $\text{CH}_2\text{Cl}_2$  to form tricyclic lactone **40** and alcohol **39**. Comparison of the sign of optical rotation of synthetic **40** with that reported in the literature (47*e*, 56) showed that when (+)-**35** was used to form

Scheme 13.



Scheme 14.



**37** (and subsequently **38**), lactone (–)-**40** was obtained (Scheme 13). This indicated that the absolute stereochemistry at C-2 in the bicyclo[2.2.1] system of **38** (Table 1) was *R* when 1*R*,5*R*,6*R*-(+)-**35** was used as the chiral auxiliary.

A drawback of using **37** ( $\text{R}=\text{CMe}_3$ ) is that both components are attached to spirodiol **35** through an ester functional group. This makes it somewhat difficult to remove the bicyclo adduct without cleaving the pivalate group as well. Although an iodolactonization provides lactone **40** and alcohol **39**, which can be recycled, lactone **40** must be treated further to regenerate the bicyclo acid. To alleviate this problem we investigated whether placing two acrylate groups on diol **35** would lead to a high de of the required bicyclo adduct. Hopefully, each acrylate would be bulky enough and adopt a conformation that would preferentially block the same face on the other acrylate. This would lead to the Diels–Alder reaction at each acrylate giving the same bicyclo adduct. Treatment of **41** with cyclopentadiene in the presence of  $\text{BCl}_3$  at  $-85^\circ\text{C}$  provided only two (**42b** and **42c**) of three possible diastereomers (Scheme 14) with a de of 76%. This was initially disappointing until we removed the bicyclo adducts from **42b** and **42c** by iodolactonization and found the %ee of the resulting mixture of was actually 89% (measured by optical rotation). The %ee was higher than the %de since three bicyclo *endo* isomers with the *S* configuration (at C-2) were formed per bicyclo *R* isomer (at C-2) in **42b** and **42c**, thereby providing **40** with an 89% ee [(88 + 88 + 12 – 12)/(88 + 88 + 12 + 12)] after iodolactonization of the mixture of diastereomers (Scheme 14).

This is as far as we have taken this project to date. Work is continuing to: (i) improve the diastereoselectivity of this latter reaction; (ii) understand better reasons for the observed absolute stereochemistry; and (iii) to increase the scope of the Diels–Alder reaction with **35** by using a variety of dienophiles, dienes, and blocking groups.

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