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Regiospecific synthesis of polysubstituted furans and their application in organic synthesis

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Abstract : The role played by 3,4-bis(trimethylsilyl)furan, 2,4-bis(trimethylsilyl)furan and 3,4-bis(tri-*n*-butylstannyl)furan as building blocks in the preparation of 2,3-disubstituted furans, 3,4-disubstituted furans, as well as 2,3,5-trisubstituted furans will be summarized. The synthetic potential of furan and its polysubstituted derivatives will be illustrated by our Diels-Alder reaction - deoxygenation route for the realization of several theoretically interesting benzenoid molecules, as well as by the preparation of 2-butenolides which are precursors of the naturally occurring prehispanolone, sphydrofuran and secosyrins.

INTRODUCTION

Though not found in animal metabolism, furan ring systems are abundantly available in secondary plant metabolites.(1) Many of these furan natural products show inspiring biological activities, such as cytotoxic and antitumor properties,(2) antispasmodic,(3) and antifeeding activities.(4) More natural furan-containing molecules continue to be uncovered at a rapid speed.(5) Due to their remarkable properties, many synthetic furans are utilized as pharmaceuticals.(1) In addition to being building blocks found in natural molecules, polysubstituted furans(6) are important precursors for the synthesis of natural and non-natural products.(7) The synthetic efforts towards polysubstituted furans belong therefore to an exceedingly active research domain. In this presentation, our own progress in the regiospecific construction of 3,4-disubstituted furans, 2,3-disubstituted furans as well as 2,3,5-trisubstituted furans will be briefly delineated. The second part of this article will then deal with the use of furan and other polysubstituted furans in the synthesis of non-natural and natural molecules.

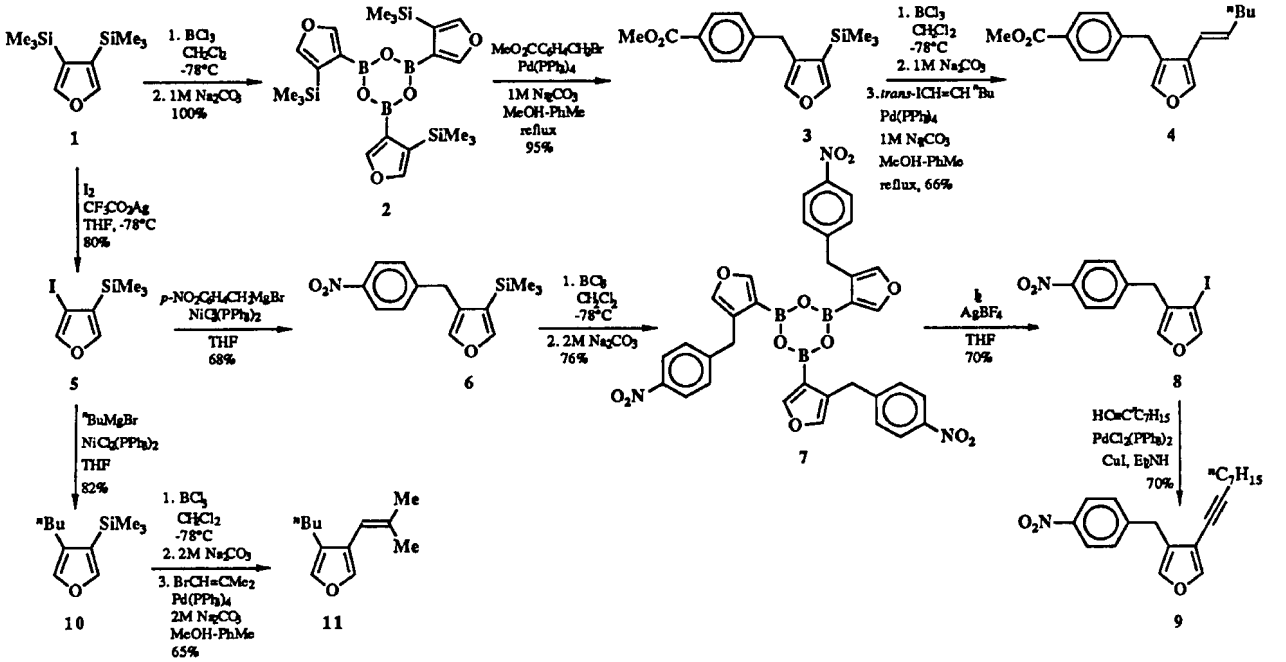
SYNTHESIS OF POLYSUBSTITUTED FURANS

(a) 3,4-Disubstituted Furans

The inclination of furans to endure lithiation and electrophilic reactions at C-2 or C-5 makes the synthesis of 3,4-disubstituted furans a rather demanding task. Although many approaches are available,(8) they are generally not suitable for furans with elaborate substituents. In our own search of a genuine access to 3,4-disubstituted furans, we reasoned that 3,4-bis(trimethylsilyl)furan (**1**)(9) could be established as a building block. Because of the well-known $(p\text{-}\sigma)_\pi$ overlap of a silyl group with its β-carbocation, an *ipso*-substitution(10) is expected to direct substituents to C-3 and/or C-4 of **1**. Some typical conversions of **1** to 3,4-disubstituted furans are depicted in Scheme 1.(9, 11-13) As can be seen, boroxine **2**(14) was obtained in a regiospecific manner and in quantitative yield from **1**.(11,13) Suzuki coupling(15) of **2** with a benzyl bromide afforded **3**, which underwent successive boroxine formation and Suzuki coupling to generate the 3,4-unsymmetrically substituted furan **4**.(11,13)

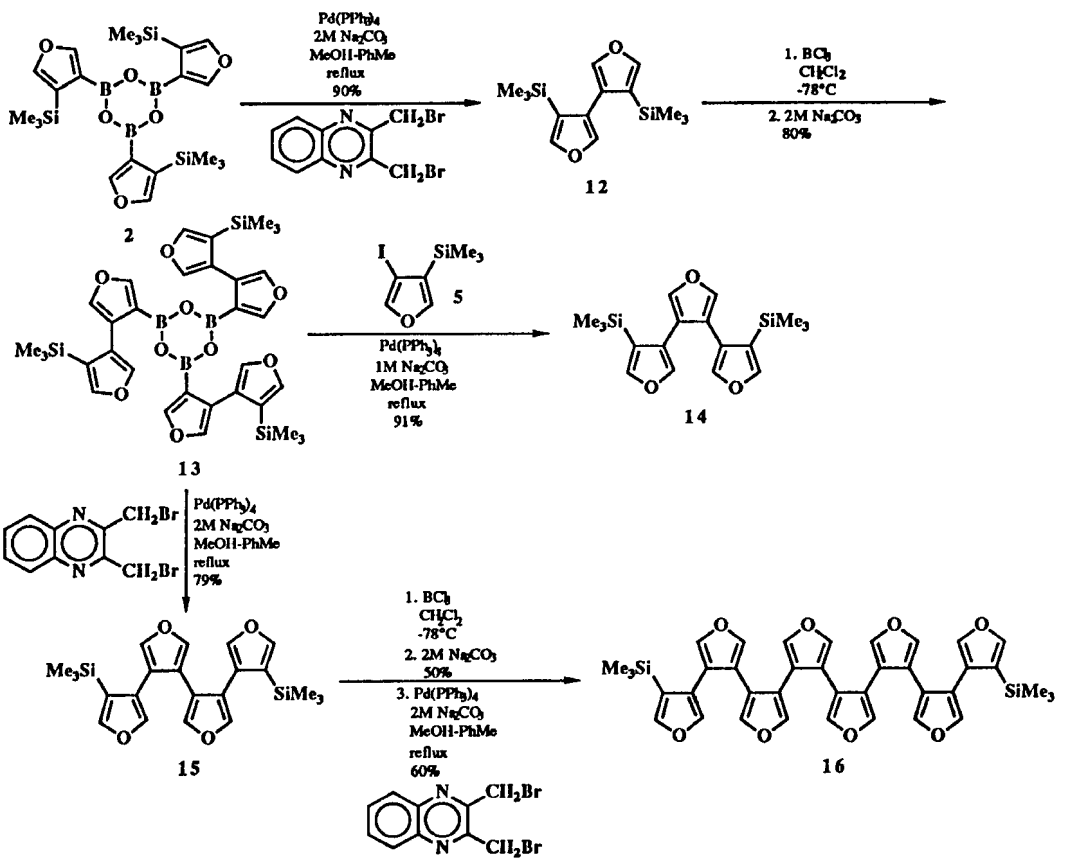
A mechanistic dilemma concerning many organometallic reactions is that the rate of β-elimination is always much faster than the transmetallation process.(16) Consequently, those alkyl groups with an sp^3 C-H β to the carbon bearing the leaving group X are notably absent from the list of organohalides used in our Suzuki coupling maneuver. In an effort to overcome this limitation, so that 3,4-dialkyl furans could also be constructed, we undertook an independent pathway whose key step is the regiospecific *ipso*-iodination of **1**.(12) The resulting iodide **5** was converted to **6** via a nickel-catalyzed coupling with a Grignard reagent. Having tried unsuccessfully to directly iodinate **6**, an indirect iodination route was sought. The second displacement of the remaining silyl group of **6** was eventually made possible through the formation of boroxine **7**, whose regiospecific *ipso*-iodination gave iodide **8**. Sonogashira reaction(17) of **8** yielded another 3,4-unsymmetrically substituted furan **9**.(12) The successful preparation of an β-C-H containing alkylfuran was demonstrated by the nickel-catalyzed reaction of iodine **5** with *n*-butylmagnesium bromide, which gave the *n*-butyl substituted furan **10**. Subsequent boroxine formation and Suzuki coupling of **10** then afforded **11**.

Scheme 1



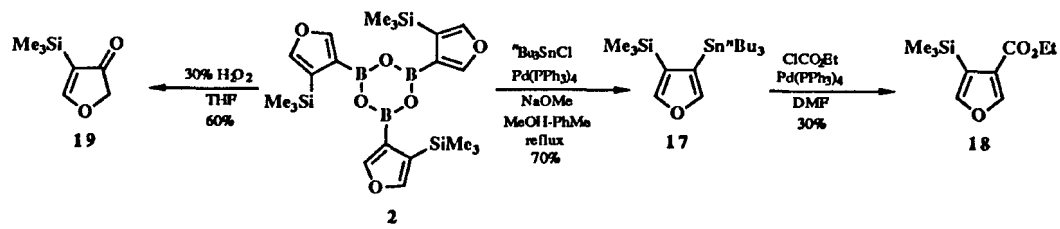
Under the Suzuki reaction condition in the presence of 2,3-bis(bromomethyl)quinoxaline, boroxine **2** unexpectedly provided a self-coupling product, namely bifuran **12** in excellent yield (Scheme 2).(18) Interestingly, **12** underwent a regiospecific boroxine formation to give **13**, which supplied a cross-coupling product terfuran **14**, as well as the self-coupling product quarterfuran **15**. A variety of symmetrical and unsymmetrical furan-3,4-diyl oligomers were synthesized in this manner.(18) It is likely that these routes will also deliver quinquefurans, sexifurans and septifurans. To put such suggestion to test, **15** was successfully transformed via a boroxine to octifuran **16**, which is the longest furan-3,4-diyl oligomer known.(18)

Scheme 2



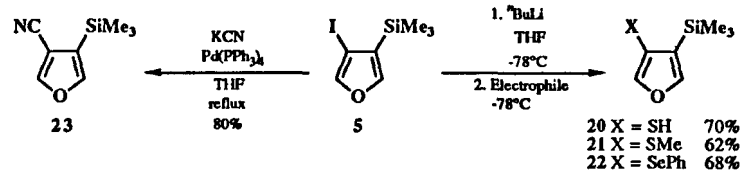
One shortcoming of the classical Suzuki reaction is that acid halides cannot be employed for the coupling purpose, because of the alkaline condition involved. However, Stille-type reactions(16,19) have successfully converted organostannyl compounds to acyl-substituted products. In order to widen the scope of our boroxine protocol, displacement of the C-B bond of boroxines with a tin functionality was sought. The reaction sequence presented in Scheme 3 is a typical example.(20,21) As shown, boroxine **2**, on treatment with tri-*n*-butylstannyl chloride under palladium-catalyzed condition, furnished the key intermediate stannane **17**. With **17** in hand, the Stille-type coupling finally gave **18**, albeit in an inferior yield (Scheme 3).(20,21) Peroxide oxidation of trimethylsilyl-substituted furans generally produced the corresponding ketones with concomitant cleavage of the C-Si bond. However, our own experience with **2** demonstrated that the reactivity of the C-B bond towards peroxide oxidation was more rapid than that of the C-Si bond, and as a result **19** was produced in an acceptable yield (Scheme 3).(20,21)

Scheme 3



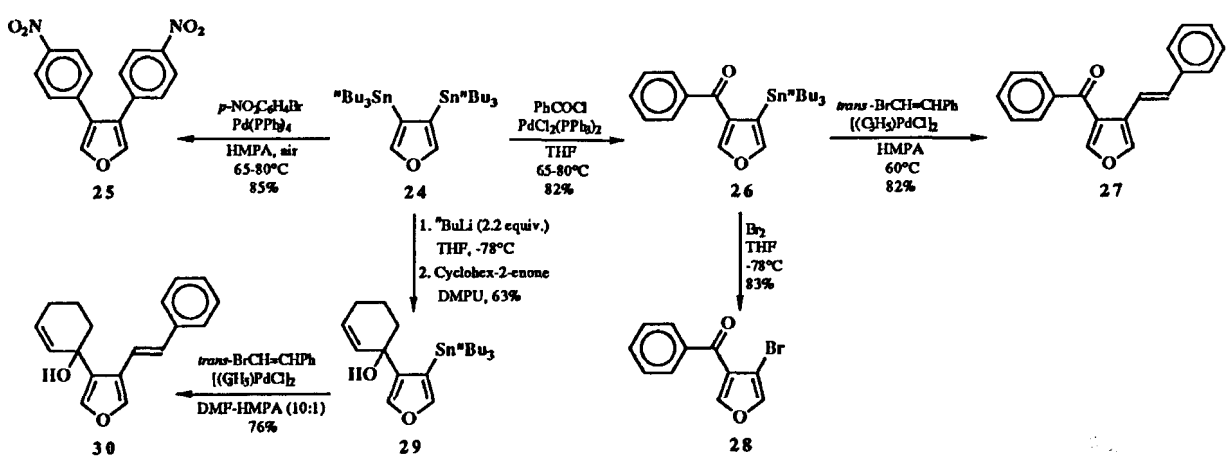
Lithiation of 3-iodo-4-trimethylsilylfuran (**5**) as expected generated the lithio intermediate, which, upon quenching with sulfur,(22) dimethyl sulfide(23) and phenylselenyl bromide,(24) afforded thiol **20**, thioether **21** and selenide **22**, respectively (Scheme 4).(25) Nitrile **23** was also obtained from **5** via a palladium-catalyzed reaction (Scheme 4).(25,26) The syntheses of fluorine-, nitrogen- and phosphorus-substituted furans from **5** and/or **2** are in progress.(25)

Scheme 4



Alternatively, the 3,4-bis(tri-*n*-butylstannyl)furan (**24**)(27-29) could also lead to 3,4-disubstituted furans, due primarily to an even larger kinetic β-effect exhibited by the stannyl groups.(30) Similar to **1**, furan **24** was also prepared via the oxazole route.(27,29) The initial palladium-catalyzed cross-coupling of **24** with *p*-bromonitrobenzene gave only the symmetrical furan **25** (Scheme 5).(27,29) However, similar reactions of **24** with benzoyl chloride yielded the monoacyl furan **26**. This partial acylation therefore provided a direct entry to 3,4-unsymmetrically substituted furans. Befitting examples to illustrate such an application were the conversion of **26** to **27** and **28**.(27,29) Another pathway from which 3,4-unsymmetrically substituted furans could be made was by soliciting a tin-lithium exchange reaction,(28,29) as shown in Scheme 5. In order to accomplish a complete replacement of one stannyl group in **24** with lithium, 2.2 equivalents of *n*-butyllithium were necessary. One of the transformations for the monolithiated furan was effected with cyclohex-2-enone, which furnished alcohol **29**. Finally, a palladium-catalyzed reaction converted **29** to **30**.(28,29)

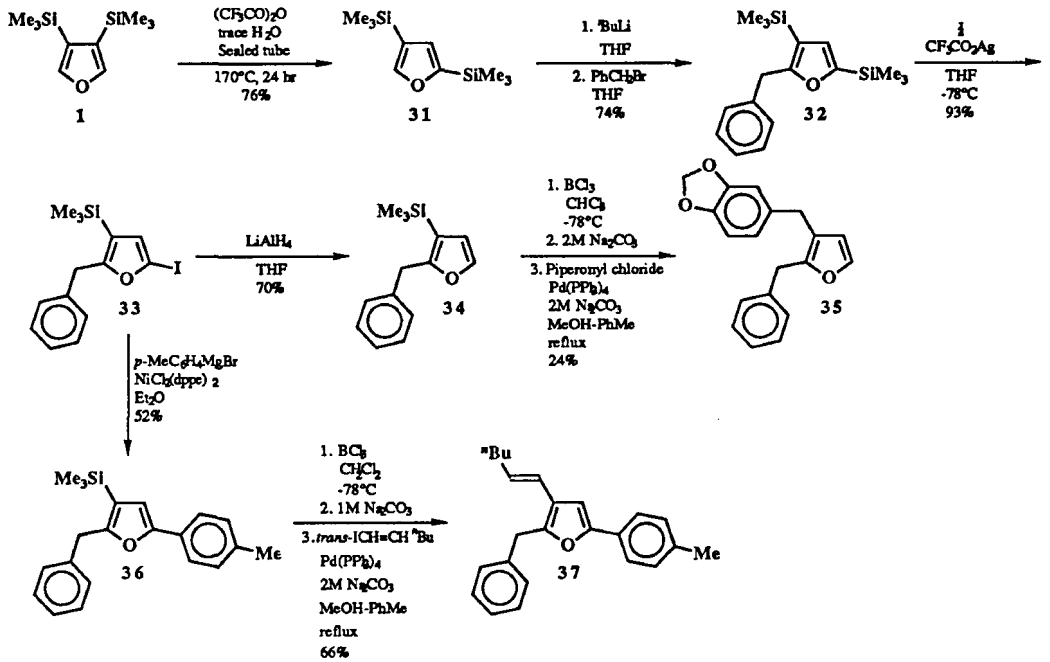
Scheme 5



(b) 2,3-Disubstituted Furans and 2,3,5-Trisubstituted Furans

Furan **1** was unexpectedly found to undergo a smooth rearrangement to form 2,4-bis(trimethylsilyl)furan (**31**) (Scheme 6),(31,32) the mechanism of which being presumably acid-catalyzed because of the trace amount of water needed. The driving force of this intriguing reaction is believed to be derived from the steric congestion of the two vicinal trimethylsilyl groups. The synthesis of 2,3-disubstituted furans(33) and 2,3,5-trisubstituted furans(34) is displayed in Scheme 6.(31) As can be seen, the trimethylsilyl at C-2 of **31** serves to block this reactive site and allows the lithiation and subsequent alkylation to occur only at C-5. Benzyl furan **32** prepared in this way was iodinated regiospecifically, generating iodide **33**, which was reduced to provide **34**. 2,3-Disubstituted furan **35** was then realized from **34** via our regular boroxine formation-Suzuki coupling approach. Alternatively, iodide **33** was also converted via **36** to the 2,3,5-trisubstituted furan **37** through consecutive nickel-catalyzed coupling as well as the boroxine formation-Suzuki coupling procedure.(31) The advantages of our methodology over those reported in the literature are its stepwise manner and its prospect of diverse substitution variety.

Scheme 6

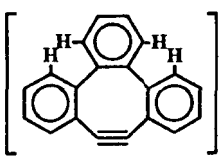


SYNTHETIC APPLICATION OF FURAN AND POLYSUBSTITUTED FURANS

(a) Synthesis of Non-natural Molecules

Examination of the recent literature revealed that there was no shortage of reports involving the use of furan and its derivatives as synthetic presursors.(7,35) Indeed, furans are extremely adaptable since they are able to serve as latent functionalities of hydropyrans,(36) 2-butene-1,4-diols,(37) carboxylic acids,(38) 2-butenolides(39) and 1,4-dicarbonyls.(40) Notwithstanding their aromatic character, furans also behave as reactive dienes for Diels-Alder cycloaddition.(41)

Our first encounter with furans stemed from our failure in isolating alkyne **38**(42) in a stable form. Such setback, nonetheless, directed us to design and to synthesize **39**, which was not expected to suffer from the detrimental peri H-H interactions as experienced by **38**. It is towards the goal of procuring **39** that an efficient synthesis of tribenzo[*a*,*c*,*e*]cyclooctene derivatives was searched. In this connection, the construction of benzenoid systems via 1,4-endoxide deoxygentaion seemed to be a genuine solution.(43) Indeed, 1,4-dimethyltribenzo[*a*,*c*,*e*]cyclooctene (**42**) was obtained in this manner as illustrated in Scheme 7.(44) Thus, dehydrobromination of dibromide **40** generated a strained alkyne,(45) which underwent Diels-Alder reaction with 2,5-dimethylfuran to form the 1,4-endoxide **41**. Low-valent-titanium deoxygenation then provided **42**.(44,46,47) Functionalization of the two methyl groups was made possible by benzylic bromination to give **43**, which was utilized for the formation of methyl ether **44**.



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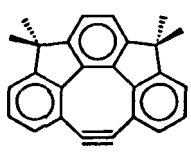

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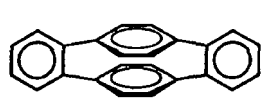

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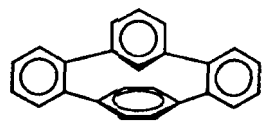

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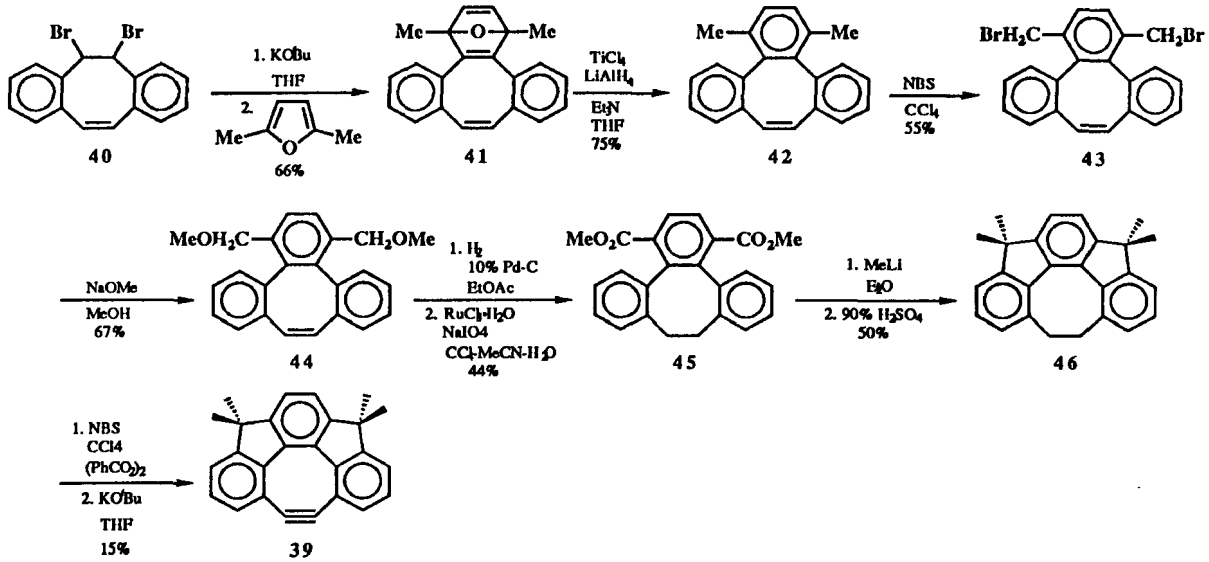
Scheme 7

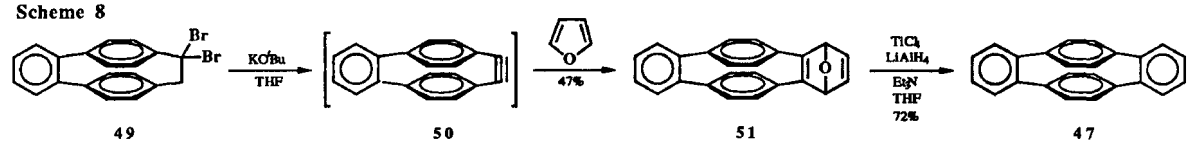


Hydrogenation of the double bond of **44** to provide **45** was necessary prior to the ruthenium tetroxide oxidation. Eventually, alcohol formation, cyclization, benzylic bromination and dehydrobromination delivered the target **39**, via **46** as the key intermediate.(48) As anticipated, **39** was very stable, forming light-yellowish crystals which melted between 203-205℃.

Novel and theoretically interesting benzenoid molecules, whose benzene rings could be constructed via the furan-endoxide-arene procedure, were our next prime targets. In light of this, dibenzo[2.2]paracyclophane (**47**) stood out as a unique molecule (Scheme 8), because its fixed geometry for orthogonal benzenes should likely be provided by virtue of its rigid molecular framework. In this regard, **47** is an impeccable model for the study of classically conjugated but orbitally unconjugated systems.(49) The tactics for the synthesis of **47** were also applied to the synthesis of dibenzo[2.2]metaparacyclophane (**48**)(Scheme 9).(50)

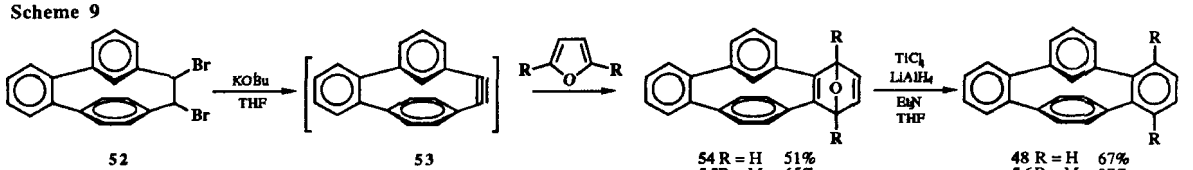
As shown in Scheme 8, the dibromide **49** was dehydrobrominated in the usual manner to give presumably the strained alkyne **50**. Expectedly, all efforts to isolate **50** as a stable compound were in vain. However, **50** was trapped by furan to form the endoxide **51**, which was deoxygenated by low-valent-titanium to give the desired target **47**.(49) The distortion of the *para*-linked benzene rings in **47** into face-to-face boat conformations was revealed by an X-ray crystallographic analysis.(51)

Scheme 8



By using exactly the same method as depicted above, dehydrobromination of **52** in the presence of furan yielded endoxide **54**. The expectedly elusive cyclophyne **53** was presumably an intermediate in this conversion. Our low-valent-titanium reagent was utilized again to transform **54** into the target cyclophane **48** (Scheme 9).(50) The most unusual phenomenon in the proton NMR of **48** was the barely observable appearance at 24℃ of a very broad coalesced signal at δ 6.95 for the four benzenoid protons of the *para*-linked benzene ring.(50) The coalescence can best be explained by a conformational inversion process,(52) which has been well established for the [2.2]metaparacyclophanes.(53) In this process, the absorptions of the four *para*-linked benzene ring protons of **48** coalesced at 24℃, due to the conformational flipping of its *meta*-bridged benzene ring. From the variable proton NMR spectrometric study, a value of 57 kJ/mole was calculated for the free energy of activation for this conformation flipping process ($\Delta G_c^{\neq}$).(50) The $\Delta G_c^{\neq}$ appears to have an intrinsic correlation with the bond types of the carbon-carbon bridges(52) as well as with the magnitude of the peri H-H repulsion between the *meta*-linked benzene and the *ortho*-bridged ones.

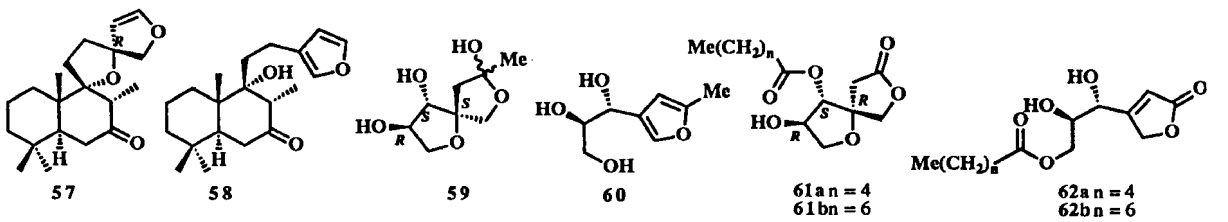
Scheme 9



In order to prove the latter argument, **55** was also obtained from **53** and 2,5-dimethylfuran. Similar deoxygenation of **55** gave the dimethylcyclophane **56**, whose interaction between the C-1 methyl and the *meta*-bridged benzene ring proton is obviously much more severe than the peri H-H interaction in **48**. As a result, the coalescence temperature of **56** was found to be higher than 140°C.(50)

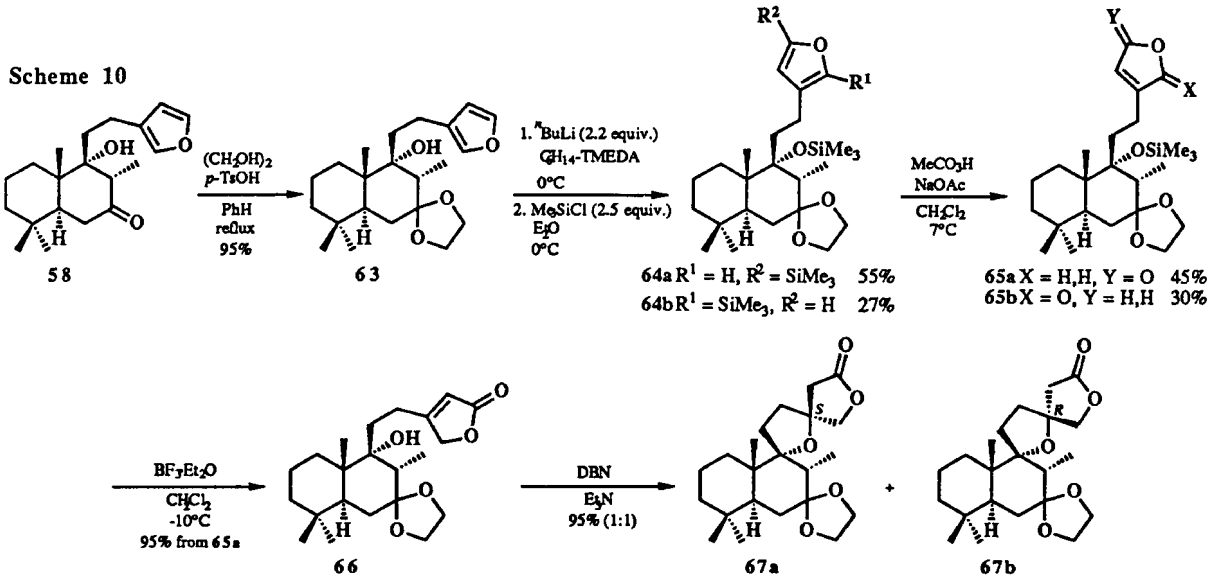
(b) Synthetic Studies of Natural Molecules: Prehispanolone, Sphydrofuran and Secosyrins

We recently isolated two diterpenes prehispanolone (**57**)(54) and hispanolone (**58**),(55) from a Chinese herb *Leonurus heterophyllus*. Interestingly, **57** is very acid labile and on treatment with dilute acid can be converted to **58** via a similar mechanism proposed by White.(56) Prehispanolone (**57**) has been found to be a specific platelet activating factor (PAF) receptor antagonist, and also exhibits some effects on the proliferation of lymphocytes.(57) It was found out that the integrity of the tetrahydrofuran ring of **57** is critical for its bioactivity. For this reason, **58** is inactive as a ligand for PAF receptor.(57) The structural relationship of sphydrofuran (**59**) and **60** is strikingly similar to that of **57** and **58**.(58) A metabolite isolated from the culture filtrate of *Streptomyces sp.* (Strain Gö 28 and Tü 3616), sphydrofuran **59** is an anomeric and ring-chain tautomeric mixture and can be easily transformed into the stable furan derivative **60** under acidic condition.(58) Of equal interesting nature are secosyrin 1 (**61a**), secosyrin 2 (**61b**), syributin 1 (**62a**) and syributin 2 (**62b**), which are unusual metabolites produced by Gram-negative bacteria expressing the class I homology group of *avrD* alleles, genes from *Pseudomonas syringae* involved with formation of bacterial signal molecules of elicitors.(59) It is of particular interest to indicate the stereochemistry of **59** and **61**, of which the absolute configuration of the spiro carbons is the only disparity. In this Section, the partial synthesis of **57** using **58** as the precursor will first be discussed, and will be followed by the synthetic studies towards **59**, **61** and **62** utilizing polysubstituted furans as starting materials.



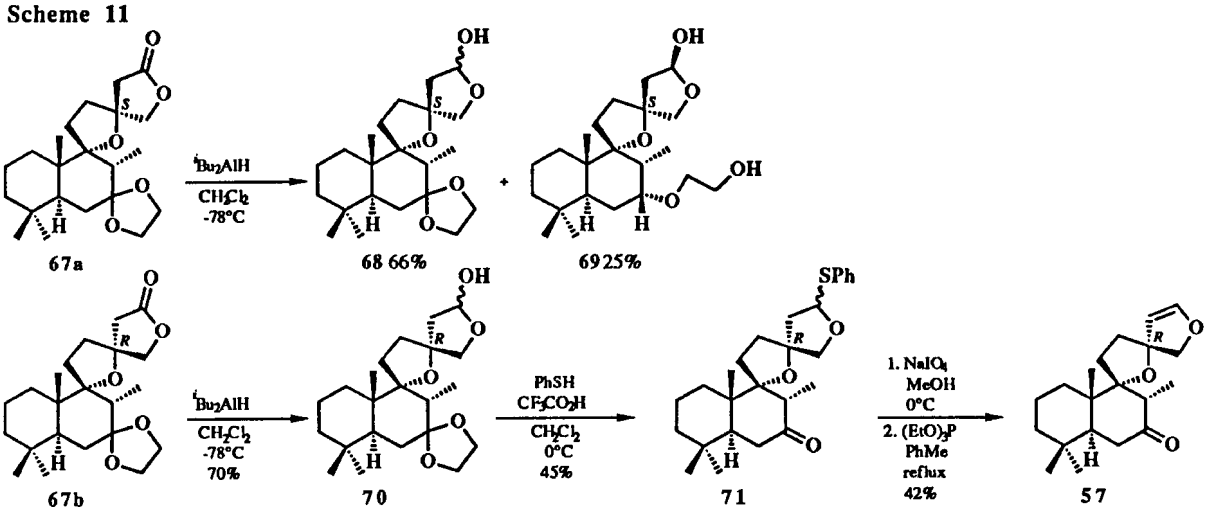
To our best knowledge, no attempt to construct the dioxaspiro framework as shown in **57** has been recorded. In view of the relative skeletal simplicity, the readily available **58** appeared to be a handy intermediate *en route* to the realization of **57**, whose synthesis is outlined in Schemes 10 and 11.(60) As can been seen, protection of the the keto group of **58** gave **63**. Deprotonation and silylation of **63** yielded a mixture of **64a** and **64b**, which was not separated and was oxidized with peracid to provide a chromatographically separable mixture of 2-butenolides **65a** and **65b**. Boron trifluoride-promoted desilylation of **65a** transformed it to the key compound **66**. An intramolecular Michael addition of **66** presumably furnished a pair of diastereomers **67a** and **67b**, the only stereochemical difference being the 13*S* or 13*R* configuration, respectively (Scheme 10).(60)

Scheme 10



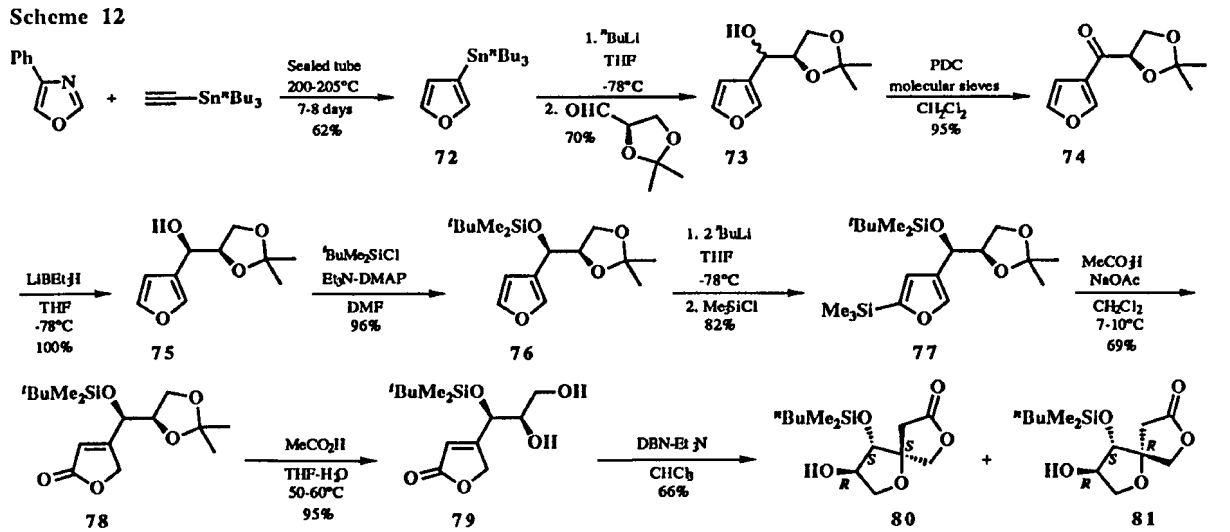
Our next step was to verify the configuration of the spiro carbons of **67a** and **67b**. Fortunately, the 13*S* configuration of **67a** was convincingly established by its DIBAL reduction, from which a mixture of **68** and a crystalline product **69** was obtained (Scheme 11). An X-ray crystallographic analysis of **69** revealed that the spiro C-13 carbon was of *S* configuration.(60) As such, the *R* configuration of the spiro carbon in **67b** was also indirectly substantiated. Indeed, **67b** was converted to **57** via a four step procedure involving DIBAL reduction, thioether formation, sulfoxide generation and thermal elimination (Scheme 11).(60) The physical and NMR spectrometric data of the synthetic **57** were identical with those of the natural **57**.(54) In order to complete the formal synthesis of **57**, a total synthesis of **64a** from the commercially available (*S*)-(+)-Miescher-Wieland ketone is in progress.

Scheme 11



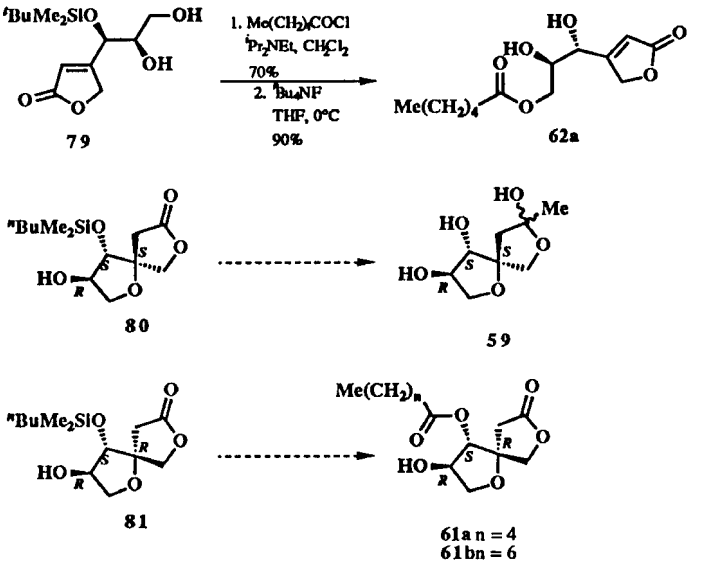
Our next target molecule was sphydrofuran (**59**), whose chemo-enzymatic synthesis was reported in 1992.(61) The initial step towards **59** required a large quantity of 3-*n*-butylstannylfuran (**72**)(Scheme 12).(62) Despite the fact that **72** has been obtained by other routes,(63) they are not suitable for a large scale preparation. Making use of our general method(9,13) involving Diels-Alder reaction between 4-phenyloxazole and tri-*n*-butylstannylacetylene and the subsequent extrusion of benzonitrile, **72** was successfully isolated in good yield as well as in multigram scale. With **72** in hand, lithiation and treatment of the resulting 3-lithiofuran with (+)-2,3-*O*-isopropylidene-*D*-glyceraldehyde gave a mixture of the *syn*- and *anti*-alcohol **73** in an approximately 1:1 ratio. In order to obtain only the *syn*-form of **73**, it was oxidized to ketone **74** and was then reduced with Super-Hydride® to **75**, which in *syn*-form. Protection of **75** gave **76**, which was converted to 2-butenolide **78** using a similar procedure as mentioned above. Thus, deprotonation and silylation of **76** generated **77**, form which **78** was procured through a peracid oxidation. Of special interest was the regiospecific deprotonation step, which provided the butenolide of the desired structure. A mild acid deprotection of **78** gave diol **79** and a base induced intramolecular Michael cyclization transformed it into a chromatographically separable mixture of **80** and **81** (Scheme 12).(62)

Scheme 12



Butenolide **62a** was obtained in two steps from **79** (Scheme 13).(62) Further conversions of **79**, **80** and **81** into other targets **62b**, **59** and **61** respectively are in progress (Scheme 13).(62) An ideal reaction condition for stereospecific Michael cyclization is also being pursued so that either **80** or **81** can be generated as the sole product.(62) Preliminary results revealed that basic amino acids such as arginine and lysine were able to enrich the amount of **81** in the product mixtures.(62)

Scheme 13



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