Total Syntheses of Naturally Occurring Molecules Possessing 1,7-Dioxaspiro[4.4]nonane Skeletons

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The syntheses of several naturally occurring molecules, namely prehispanolone, sphydrofuran, secosyrins, and syringolides are reviewed. Interestingly, these compounds are all structurally related, possessing a 1,7-dioxaspiro[4.4]nonane framework. The pivotal step in these synthetic endeavors involves the peracid oxidation of substituted 2-trimethylsilylfurans to but-2-en-4-olides. A subsequent intramolecular Michael addition procedure was also essential in the construction of the spiro skeleton. Two significant issues concerning regioselectivity and stereoselectivity are also addressed.

Introduction

Prehispanolone (**1**), a labdane diterpene, has been isolated in this laboratory from the aerial parts of the Chinese herbal medicine Yi Mu Cao (*Leonurus heterophyllus*).[1] Using an in vitro radioligand binding assay for the platelet activating factor (PAF) receptor, **1** was identified as a specific PAF receptor antagonist.[2][3] As can be seen in Scheme 1, the most significant structural feature of **1** is its 1,7-dioxaspiro[4.4]non-8-ene unit. It is noteworthy that a mild acid hydrolysis[1][4] of **1** converted it to the PAF-receptor-inactive 3-substituted furanoid hispanolone (**2**).[3][5] The aforementioned structural key unit 1,7-dioxaspiro[4.4]non-8-ene and its saturated analog 1,7-dioxaspiro[4.4]nonane, as depicted in Scheme 1, are also found in a number of other natural products. For example, sphydrofuran (**3**) is a structurally intriguing secondary metabolite produced by actinomycetes, and which was first isolated by the Umezawas and their co-workers from the culture filtrate of the strains MC41-M1 and MC340-A1 by a chemical screening method using the Ehrlich′s reagent.[6] Sphydrofuran (**3**) exists as an anomeric and ring-chain tautomeric mixture, and, in the same way as **1**, can easily be transformed into the stable 2-methyl-4-(1-glyceryl)furan (**4**) under very mild acidic conditions. Up to now, no bio-activity of **3** towards various organisms has been detected, but under the influence of **4**, a growth promotion for some bacteria and viruses has been found.[7] Although the structures of **3** and **4** were established in 1971,[6] their absolute configurations have only been assigned not long ago.[7] Another class of naturally occurring compounds, comprising secosyrin 1 (**5a**) and secosyrin 2 (**5b**), as well as syributin 1 (**6a**) and syributin 2 (**6b**), constitute the major co-products of the elicitors (signal molecules) syringolide 1 (**7a**) and syringolide 2 (**7b**). As can be seen, these molecules all possess stereochemical features that resemble those of either **1** and **3** or **2** and **4**. These unusual metabolites **5**, **6**, and **7** were isolated and structur-

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Henry Wong was born in 1950 and grew up in Hong Kong. He studied chemistry at the Chinese University of Hong Kong and in 1976 he obtained his Ph.D. degree from University College London under the supervision of the late Franz Sondheimer. After spending two years at Harvard University as a postdoctoral fellow with the late Robert B. Woodward, he began his independent research career as Ramsay Memorial Fellow at University College London. After working for two years at the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences, he returned to Hong Kong where he is currently Professor of Chemistry at the Chinese University of Hong Kong. His current research interests include the use of organosilicon compounds in organic synthesis and the synthesis of non-natural and natural molecules.

MICROREVIEWS: This feature introduces the readers to the authors′ research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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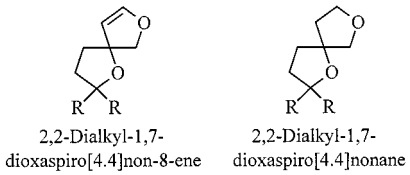
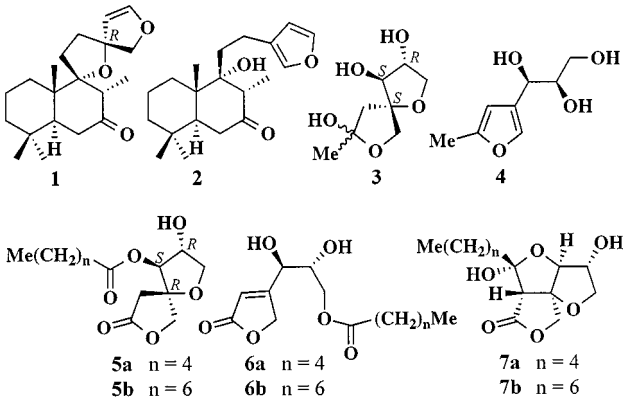
ally elucidated by Sims and his co-workers.[8] It was reported that the novel non-proteinaceous *C*-glycosidic elicitors syringolides **7** are produced extracellularly from the plant pathogen *Pseudomonas syringae* pv. *tomato* by the bacterial expressing avirulence gene D (*avrD*).[8][9] When this pathogen attacks the soybean plants carrying the disease-resistance gene *Rpg4*, the elicitors can be recognized and accordingly a hypersensitive defence response (HR) involving fast, localized cell death followed by accumulation of the antimicrobial phytoalexins around the infected site will be triggered.[8][9] Secosyrins **5** and syributins **6** are not active elicitors, but are of biosynthetic importance because they are produced alongside with **7**. Biogenetically, compounds **5** are formally related to **7** through a reverse Claisen cleavage, while **6** can be generated from **5** by a retro Michael reaction followed by a 1,3-acyl migration.



Scheme 1. The dioxaspiro[4.4]nonanoid skeletons



Apparently, there have been as yet no previous concerted efforts to construct compounds containing 1,7-dioxaspiro[4.4]non-8-ene or 1,7-dioxaspiro[4.4]nonane frameworks.[10] This is in spite of the fact that these spiro moieties are common structural units, not only occurring in the aforementioned molecules, but also in their related compounds, such as nepetaefolin,[4] premarrubiin,[11a] prerotundifuran,[11b] premarrubenol,[11c] precalyone,[11d] pregaleopsin,[11e] preperegrinine,[11f] pregaleuterone,[11g] and preleoheterin,[11h] as well as in other natural products such as leucodrin,[12] conocarpin,[13] piptoside,[14] leudrin,[15] hyperolactone,[10l,16] and cinatrin A.[17] In view of the structural challenge and unique nature of these spiro compounds and their derivatives, a unified synthetic approach has been designed and realized in this laboratory with the aim of constructing the dioxaspiro[4.4]nonane and dioxaspiro[4.4]nonene skeletal units. In this Microreview, I would like to give a summary of our efforts directed towards the total syntheses of compounds **1**−**7**.

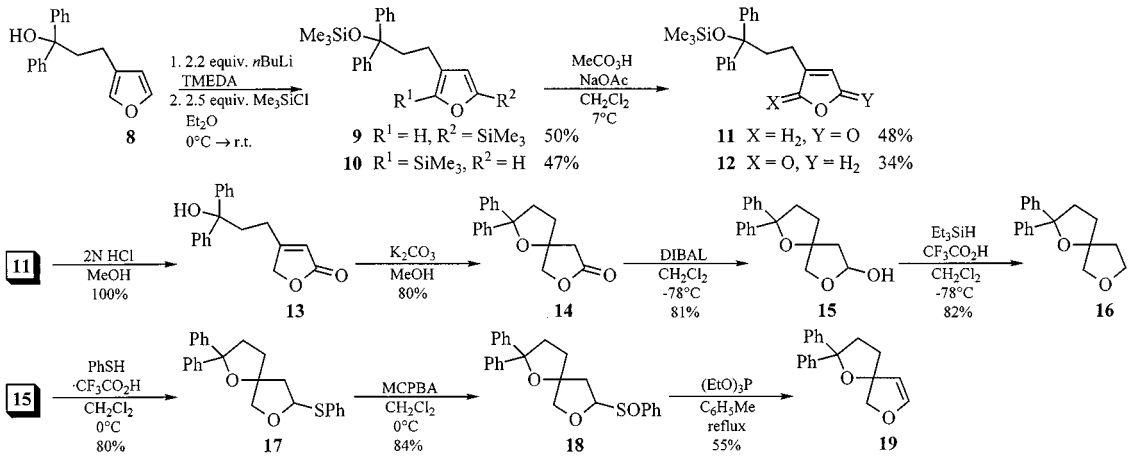
Model Study[18,19]

A structural examination of prehispanolone (**1**) and hispanolone (**2**) revealed that **2** may be a key intermediate en route to the total synthesis of **1**. For assessment purposes, a model study was first undertaken in which several model compounds, which possess similar skeletal units as those of **1** and **2**, were constructed. It was also expected that the same strategy could be adopted for the construction of **3**−**7**. As outlined in Scheme 2, the furan derivative **8**,[18][20] prepared in a straightforward manner from 3-furoic acid,[20] was subjected to undergo a deprotonation−silylation procedure.[21] The resulting silylated products **9** and **10** were generated in an approximately 1:1 ratio (by ^{1}H-NMR spectroscopy). An approach leading towards a more regioselective silylation will be discussed in the next section (vide infra). Without further separation, the a mixture of **9** and **10** was oxidized with peracid[22] to afford the chromatographically separable butenolides **11** and **12** in 48% and 34% yield, respectively. Desilylation of **11** under mildly acidic conditions furnished the hydroxybutenolide **13** in an almost quantitative yield.[23] With the key compound **13** at hand, the crucial intramolecular Michael addition could then be investigated. It was eventually found that when **13** was treated with K_2CO_3 in MeOH according to the procedure previously employed to prepare methyl *N*-(*tert*-butoxycarbonyl)galantinate and its C-3 epimer starting from (5*S*,6*S*)-methyl 6-(*tert*-butoxycarbonylamino)-5,7-dihydroxy-2-heptenoate,[24] we were able to achieve the construction of the dioxaspiro[4.4]nonanoid framework **14**, which was reduced in two steps[25][26] via **15** to afford one of the two model compounds, namely 2,2-diphenyl-1,7-dioxaspiro[4.4]nonane (**16**). Following this success in preparing **16**, a similar protocol was adopted in an attempt to convert lactol **15** to an unsaturated spiro ether. By employing Ley's procedure,[27] phenyl sulfide **17** was prepared, a subsequent oxidation of which gave the phenyl sulfoxide **18**. The latter underwent an elimination to yield the other model compound 2,2-diphenyl-1,7-dioxaspiro[4.4]non-8-ene (**19**).

As depicted in Scheme 2, compounds **8** and **19** contain all the functional group characteristics found in those of hispanolone (**2**) and prehispanolone (**1**), respectively. Thus, the multi-step conversion of **8** into **16** and **19** might serve as a prototype for our general synthetic strategy.

Total Synthesis of Hispanolone (2) and Prehispanolone (1)[18,28]

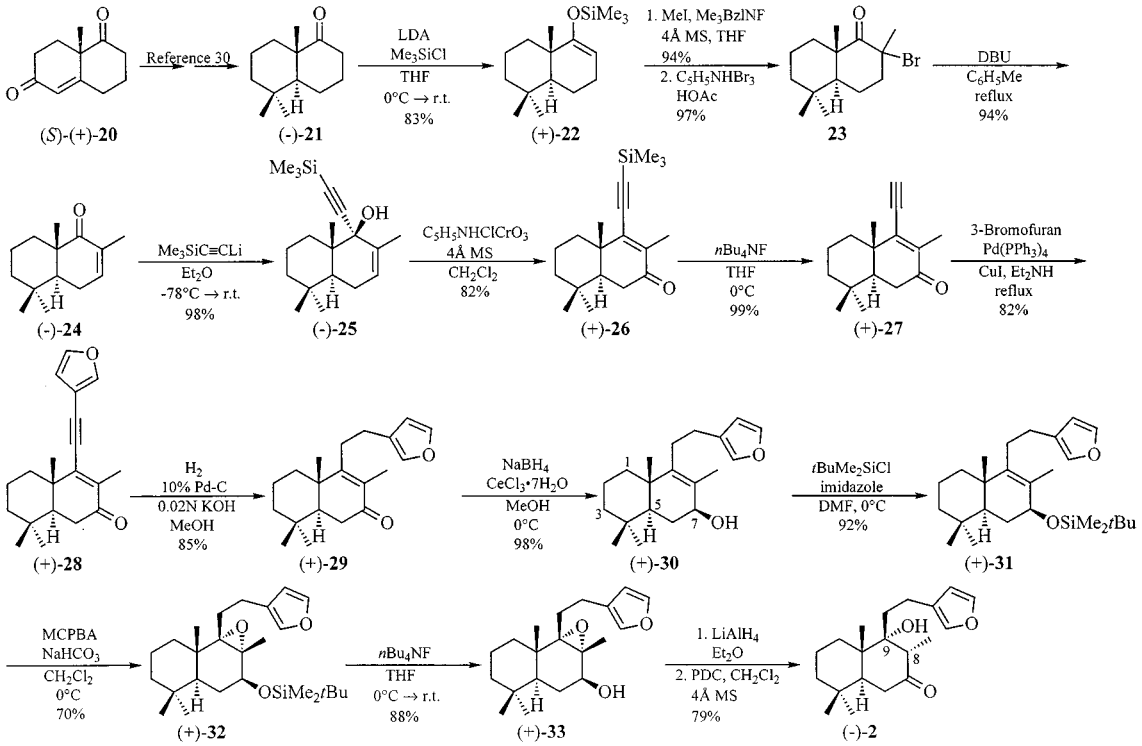
Having secured a reliable route for the synthesis of model compound **19** from **8**, analogous procedures were then applied for the construction of the target molecule **1**. The synthesis of naturally occurring (−)-hispanolone (**2**) in highly enantiomerically enriched form as the key intermediate is illustrated in Scheme 3.[28] As shown, the commercially available (*S*)-(+) Wieland−Miescher ketone (**20**) was converted into ketone (−)-**21** by following a modification of a method first reported by Sondheimer and Elad.[29][30] In a



Scheme 2. Synthesis of **16** and **19**

first attempt to introduce a methyl group into (−)-**21**, the seemingly straightforward monomethylation using LDA and MeI led only to a mixture of mono- and dimethylated products. To circumvent the need for a tedious chromatographic separation, a two-step route[31] was employed. Thus, (−)-**21** was first converted into the silyl enol ether (+)-**22**, which was then subjected to undergo a concomitant desilylation and methylation, furnishing the monomethylated compound in 94% yield. Bromination of this compound with pyridinium bromide perbromide in acetic acid[29b] generated the bromide **23** as a diastereomeric mixture, which was not separated but was treated immediately with DBU to give the homochiral enone (−)-**24**.[32] After a 1,2-addition of lithium trimethylsilylacetylide to (−)-**24**, the resulting tertiary alcohol (−)-**25** was subjected to a 1,3-hydroxy shift and subsequent oxidation with PCC[33] to provide the enone (+)-**26** in a good overall yield. Fluoride-induced desilylation of (+)-**26** gave the unstable terminal alkyne (+)-**27**, which was found to decompose gradually within 48 h at room temperature. Immediately after (+)-**27** was purified by column-chromatographic purification, (+)-**27** was allowed to react with 3-bromofuran under the Sonogashira coupling reaction conditions,[34] to afford the 3-substituted furan (+)-**28** in 82% yield. The triple bond in (+)-**28** was hydrogenated in the presence of 10% palladium on charcoal[35] to provide the known enone (+)-**29**,[36] the specific rotation of which was measured as $[\alpha]_D^{25} = +40.8$ (c = 2.80, $CHCl_3$), in good agreement with the literature value[36a] $[\alpha]_D^{20} = +39.7$ (c = 1.12, $CHCl_3$). The structure of (+)-**29** was also further confirmed by comparison of its ^{1}H-NMR, ^{13}C-NMR, and mass spectra with those of the authentic compound.[36] It is interesting to note that (+)-**29** has previously been obtained by dehydration of hispanolone (**2**).[36] Despite much experimentation, enone (+)-**29** was proved to be inert to all Weitz−Scheffer epoxidation conditions,[37] presumably due to the steric hindrance of the tetrasubstituted alkene. Another means by which (+)-**29** could be converted into (−)-**2** would be to follow a multistep pathway. Thus, the synthesis of hispanolone (**2**) was completed by reduction of the carbonyl group in (+)-**29** with the Luche reagent,[38] and was followed by hydroxy group protection of the resulting (+)-**30** as the *tert*-butyldimethylsilyl ether (+)-**31**. From the ^{1}H-NMR spectrum, the hydroxy group of (+)-**30** could be assigned a β configuration due to the appearance of a triplet at δ = 4.10 (J = 8.1 Hz, 7-H). The carbon−carbon double bond of (+)-**31** was successfully epoxidized by using *m*-chloroperoxybenzoic acid under buffered conditions,[39] leading to the desired α-epoxide (+)-**32** in 70% yield, together with 17% yield of the undesired β-epoxide. After desilylation, the resulting alcohol (+)-**33** was reduced with lithium aluminum hydride[40] to afford a diol, which was not purified further, but was oxidized directly to give the target hispanolone (**2**). The synthetic **2** possessed a specific rotation $[\alpha]_D^{25} = -18.3$ (c = 0.64, $CHCl_3$), which was almost identical to that reported in the literature[3,11h] {$[\alpha]_D^{22} = -18.2$ (c = 1.00, $CHCl_3$)}. Moreover, the spectroscopic data of synthetic (−)-**2** are in full agreement with those of the naturally occurring hispanolone (**2**).[1] The inherent advantage of this epoxide reduction route lies in the stereospecific creation of the 8-α-methyl group as well as the 9-α-hydroxy group in one step.

The synthesis of prehispanolone (**1**) was commenced once a sizeable supply of (−)-**2** had been secured.[18] As depicted in Scheme 4, protection of the carbonyl group of (−)-**2** gave (+)-**34** in 95% yield. The regioselective deprotonation and silylation of (+)-**34** was the most crucial step of this strategy. Previously, it was found that treatment of (+)-**34** with an excess of *n*BuLi and trimethylsilyl chloride gave a mixture of *C*-silylated and *O*-silylated products, which required a tedious chromatographic separation.[18] Moreover, the trimethylsiloxy product generated in this way needed an extra desilylation step that would inevitably have been detrimental to the overall yield.[41] After much experimentation, it was finally discovered that 3.5 equivalents of *n*BuLi converted (+)-**34** to presumably a bis(lithium) salt, which, upon treatment with only 0.7 equivalents of trimethylsilyl chloride, furnished the sterically less demanding (−)-**35** as the sole product, together with the recovered starting material.[28b] The total reacted yield of this special pro-

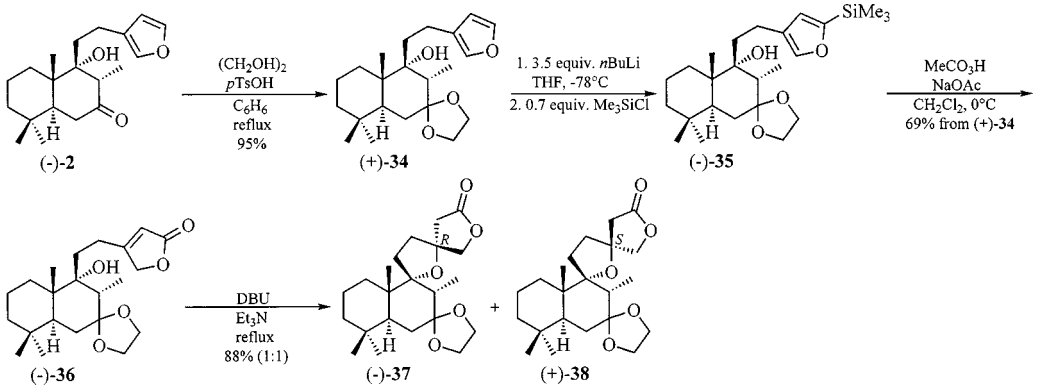


Scheme 3. Synthesis of hispanolone (−)-(**2**)

cedure was found to be quite acceptable and a subsequent peroxy acid oxidation gave the butenolide (−)-**36** in 69% overall yield based on (+)-**34**. The intramolecular conjugate addition reaction[42] of (−)-**36** is of substantial synthetic importance because it would produce a pair of diastereomers, (−)-**37** and (+)-**38**, differing only in their (13*R*) and (13*S*) configurations. Refluxing of a mixture of (−)-**36**, DBU, and Et_3N under reflux was found to furnish a 1:1 mixture of (−)-**37** and (+)-**38** in 88% yield. Unlike the cyclization of **13**, it is noteworthy that a similar reaction of (−)-**36** with potassium carbonate in methanol[24] led only to an inferior yield of (−)-**37** and (+)-**38**. Compounds (−)-**37** and (+)-**38** were conveniently separated by column chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 8:1).

spiro carbon atom (C-13) in (−)-**1** is probably also non-enantiospecific, because two related compounds, namely scutellone B and scutellone G, have been isolated and identified.[43] The (13*S*) configuration of (+)-**38** was unequivocally established by an X-ray crystallographic analysis of **40**, which was produced as a side product upon DIBAL reduction of (+)-**38**, the major product being **39** (66%) (Scheme 5).[18]

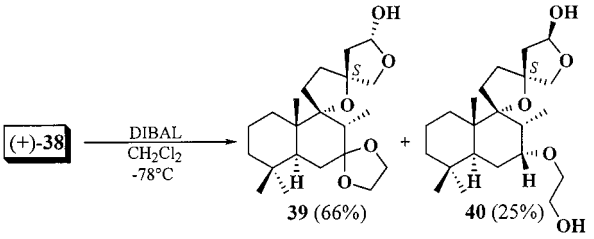
In principle, the verification of the (13*S*) configuration of (+)-**38** also indirectly confirmed the (13*R*) configuration of (−)-**37**. Despite numerous experimental trials employing various bases in achiral or chiral forms,[28b] so far it has not been possible to force the Michael cyclization of (−)-**36** towards a higher proportion of the desired (−)-**37**. To



Scheme 4. Synthesis of (−)-**37** and (+)-**38**

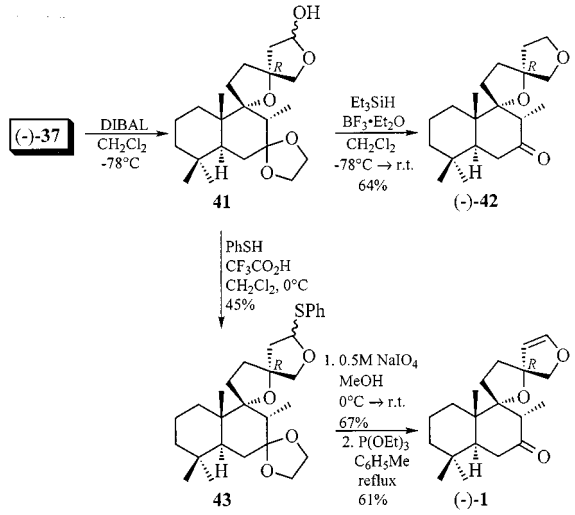
It is significant to note that the biosynthetic pathway responsible for determining the absolute configuration at the

complete the total synthesis, (−)-**37** was reduced with DIBAL to give the lactol **41**. The dioxaspiro[4.4]nonane ana-



Scheme 5. Synthesis of **39** and **40**

log (−)-**42** was obtained from **41** by silane reduction, which was accompanied by concomitant deprotection of the ketal group, presumably due to the Lewis acidic conditions. The physical and spectroscopic data of (−)-**42** were identical to those of an authentic sample prepared by catalytic hydrogenation of natural (−)-**1**. Again, a modification of Ley's procedure[27] was applied to the synthesis of (−)-**1**. Thus, **41** was transformed into the sulfur acetal **43**, which was oxidized with sodium periodate to give the corresponding sulfoxide intermediate, elimination of which eventually provided prehispanolone (−)-**1** in 61% yield. The physical and spectroscopic data of the product were identical to those of natural (−)-**1**, with $[\alpha]_D^{25} = -64.6$ ($c = 0.85$, C_6H_6), which is comparing well with the literature value {$[\alpha]_D^{22} = -63.6$ ($c = 0.55$, C_6H_6)}.[1]



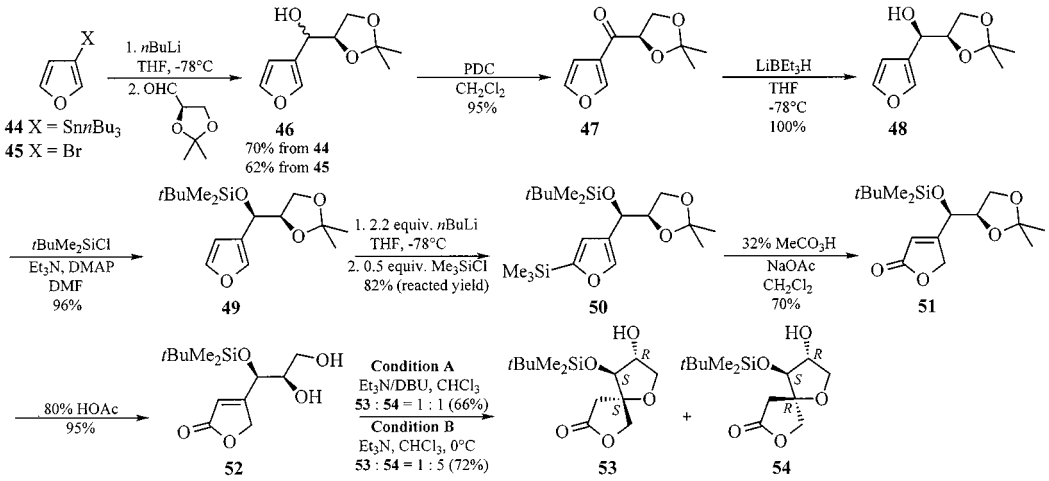
Scheme 6. Synthesis of prehispanolone (−)-**1**

Total Synthesis of Sphydrofuran (3) and 2-Methyl-4-(1-glyceryl)furan (4)[44a]

In 1992, Schmid[45] reported the synthesis of sphydrofuran (**3**) from achiral precursors following a chemo-enzymatic pathway. Very recently, Rizzacasa also reported an approach to **3** by involving the Ireland−Claisen rearrangement as a pivotal step.[46] By treating **3** with a large excess of sodium methoxide, Rizzacasa also observed the intriguing formation of a thermodynamically more stable spiro epimer of **3**, which he termed "isosphydrofuran", when **3** was allowed to react with a large excess of sodium methoxide.[46]

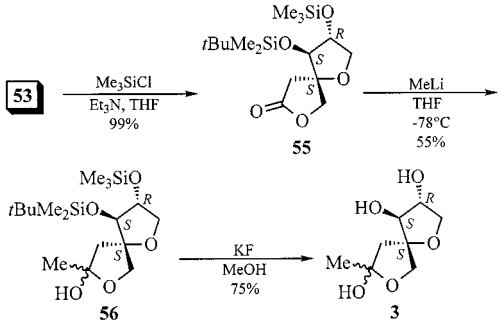
As shown in Scheme 7, the synthetic pathway towards **3** adopted in this study started from 3-tri-*n*-butylstannylfuran (**44**), which had previously been obtained in this laboratory as a side product of the reaction between bis(tri-*n*-butylstannyl)acetylene and 4-phenyloxazole.[47] A more target-oriented approach was achieved by heating a mixture of tri-*n*-butylstannylacetylene and 4-phenyloxazole in a sealed tube at 200 °C for 9 d, giving **44** in 38% yield and in multigram quantities.[48] Alternatively, 3-bromofuran (**45**)[49] could also be utilized as the precursor.[44a] Both **44** and **45** could be converted into 3-lithiofuran by reaction with *n*BuLi at −78°C. Quenching of the lithium salt with the homochiral (+)-2,3-*O*-isopropylidene-D-glyceraldehyde[50] according to Jurczak's procedure[51] gave a known[52a] 1:1 *syn*- and *anti*-isomeric mixture **46** in a 1:1 ratio,[52] which was not separated but was oxidized directly with PDC to afford ketone **47**.[53] On Reduction of **47** with Super-Hydride, **47** gave an excellent yield of *syn*-**48** as the only isolable product. After protection of **48**, the *tert*-butyldimethylsilyl ether **49** was deprotonated with 2.2 equivalents of *n*BuLi and the resulting, presumably dilithiated salt was quenched with 0.5 equivalents of trimethylsilyl chloride to give the desired sterically less encumbered monosilylated **50** in 82% reacted yield, together with some recovered starting **49**. This remarkable regioselectivity is in line with the previous observations (vide supra) and again most likely stems from the sterically hindered *tert*-butyldimethylsiloxy group. Eventually, oxidation of **50** with peroxyacetic acid in the presence of sodium acetate furnished butenolide **51**, from which the acetonide protecting group was removed by acid hydrolysis, giving the diol **52** in good yield. To construct the dioxaspiro framework, a base-induced conjugate addition reaction was employed as the crucial step. In this manner, **52** underwent cyclization to a 1:1 mixture of diastereomers **53** and **54** when Et_3N/DBU in chloroform was used, while a much better stereoselectivity (1:5) was achieved using just Et_3N in chloroform. The separation of **53** and **54** was easily accomplished by column chromatography on silica gel. Lactone **53** formed single crystals suitable for an X-ray diffraction study,[44a] which verified its absolute configuration as being compatible with that of sphydrofuran (**3**). With this information at hand, the absolute stereochemistry of **54** could indirectly be assigned (Scheme 7), and which confirmed that this compound could serve as a precursor of secosyrins (**5**) (vide infra).

Once the absolute structures of **53** and **54** had been confirmed, our efforts could then be directed towards the total synthesis of **3** (Scheme 8) and **4** (Scheme 9). Thus, protection of the remaining hydroxy group on **53** provided **55**, which was allowed to react with an excess of methyllithium at −78°C[54] to give **56**. The preparation of **3** was completed by employing a mild desilylation reaction. Sphydrofuran (**3**) {$[\alpha]_D^{20} = +16.1$ ($c = 0.26$, H_2O)} was separated conveniently by chromatography on a silica gel column in 75% yield. The specific rotatory power of **3** was identical to that reported in the literature {$[\alpha]_D^{20} = +16$ ($c = 0.5$,



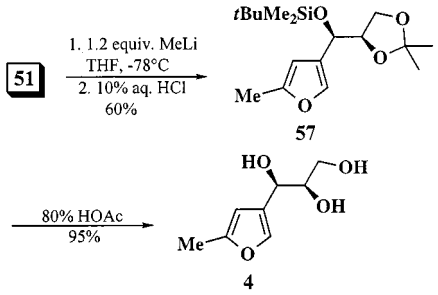
Scheme 7. Synthesis of **53** and **54**

H_2O)}.[7] All other analytical and spectroscopic data are in full agreement with those of samples of **3** obtained from natural[6][7] and synthetic sources.[45][46]



Scheme 8. Synthesis of sphydrofuran (**3**)

The furan co-product **4** could easily be obtained from **3** under mildly acidic conditions.[6] Synthetically, treatment of butenolide **51** with methyllithium and subsequent dehydration with 10% HCl yielded furan **57**, which could be deprotected with acetic acid to produce **4** in good overall yield (Scheme 9).



Scheme 9. Synthesis of **4**

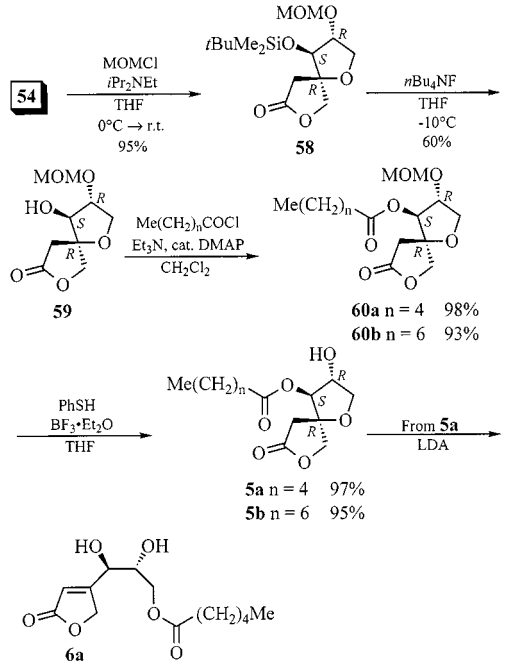
Total Synthesis of Secosyrins (5) and Syributins (6)[44a]

Total syntheses of secosyrin 1 (**5a**),[55] secosyrin 2 (**5b**),[55b] syributin 1 (**6a**),[55b,56] and syributin 2 (**6b**)[55b] have all very recently been reported in the literature. With **54** (Scheme 7) at hand, the approach used in this laboratory for the total synthesis of **5** (Scheme 10) and **6** (Scheme 11) will now be summarized.[44a]

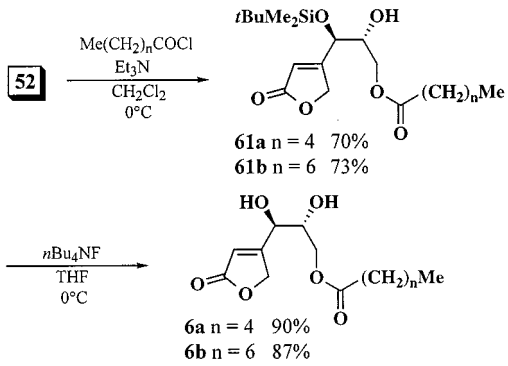
As illustrated in Scheme 10, the secondary hydroxy group in **54** was first protected as a methoxymethyl ether.[57] The *tert*-butyldimethylsilyl group of the resulting lactone **58** was then removed with TBAF in THF, to give alcohol **59**. Subsequent esterification of **59** with either hexanoyl chloride or octanoyl chloride then furnished the esters **60a** and **60b**, respectively. Finally, a mixture of thiophenol and boron trifluoride–diethyl ether was utilized to remove the methoxymethyl protecting groups from **60a** and **60b**,[58] furnishing the target molecules, namely secosyrin 1 (**5a**) and secosyrin 2 (**5b**), respectively. The physical and spectroscopic data of **5a** and **5b** are in full agreement with those reported in the literature.[8] It is noteworthy that the values reported in the literature[55] for the specific rotatory power of secosyrin 1 (**5a**) are higher than that of **5a** prepared from **54** in this laboratory. Interestingly, treatment of secosyrin 1 (**5a**) with lithium isopropylamide cleanly provided syributin 1 (**6a**), presumably by way of a reverse Michael ring-fission pathway, with a subsequent 1,3-acyl migration (Scheme 10).[44b] In a more straightforward and chemospecific manner, syributin 1 (**6a**) and syributin 2 (**6b**) could also be prepared from **52** (Scheme 11).[44a] Thus, esterification of **52** with either hexanoyl chloride or octanoyl chloride under basic conditions gave esters **61a** and **61b**, respectively. Deprotection of these silyl ethers gave the desired syributin 1 (**6a**) and syributin 2 (**6b**), the physical and spectroscopic data of which were identical to those of the naturally occurring syributins reported in the literature.[8]

Total Synthesis of Syringolides (7)[59]

Syringolides 1 (**7a**) and 2 (**7b**), both being avirulence gene D (*avrD*) specified hypersensitive defence response elicitors, have been synthetic targets of a number of research teams. Indeed, a literature survey revealed that, since 1996 at least



Scheme 10. Synthesis of secosyrins **5a** and **5b**

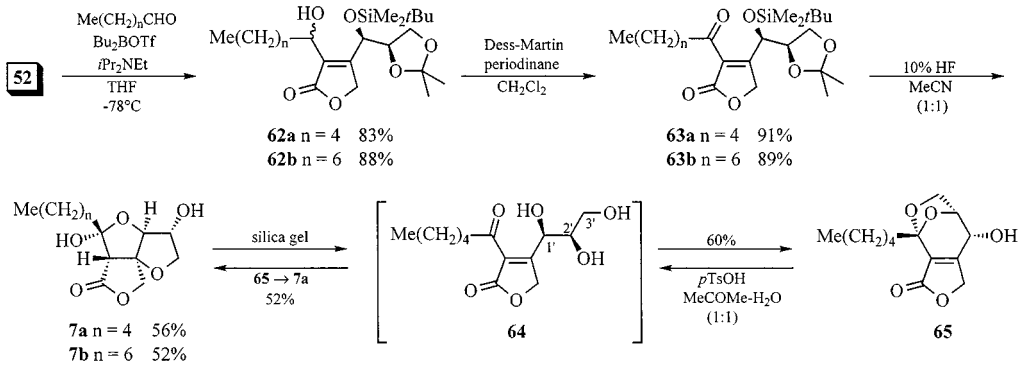


Scheme 11. Synthesis of syributins **6a** and **6b**

seven total syntheses of **7a** and/or **7b** have been reported.[56][60] Some of these endeavors started from achiral precursors and chirality was introduced by making use of the Sharpless asymmetric dihydroxylation (AD).[56,60e,60f] An earlier synthesis of both enantiomers of **7a** and **7b** was achieved by employing the antipodes of 2,3-*O*-isopropylidenethreitol as starting materials.[60a] Another synthesis employing derivatives of L-threitol has also been reported.[60b,60c] D-Xylulose acetonide,[60d] D-xylose,[60g] and xylofuranose[60h] have all been used as homochiral precursors in the syntheses of **7a** and/or **7b**. Before presenting the results of the synthesis of **7a** and **7b** in this laboratory, it is noteworthy to point out that the aforementioned syntheses shared a common setback in that only relatively poor yields (6−23%) were achieved in the final ring construction step.[56][60] In the light of this fact, new routes to **7a** and **7b** were sought, the procedures of which are outlined in Scheme 12. Attempts to prepare **62a** and **62b** from **52** by means of the Baylis−Hillman reaction were unsuccessful.[61] As can be seen in Scheme 12, the pivotal ketones **63a** and **63b** were also procured at length by employing Honda′s procedure[56] as well.[59] In view of the failure to obtain syringolides (**7**) in acceptable yields, as mentioned above, milder cyclization conditions were investigated. After a number of unsuccessful trials, 10% HF in acetonitrile was finally chosen to deprotect the silyl and acetonide groups of **63a** and **63b**, as well as to induce the subsequent conjugate addition and acetal formation.[59] Extreme care must be taken during the silica gel chromatographic separation of syringolide 1 (**7a**) and syringolide 2 (**7b**). Flash chromatography on a short silica gel column followed by careful recrystallization provided **7a** and **7b** in reproducible 56% and 52% yield, respectively. On the other hand, a normal column chromatography on silica gel after the 10% HF reaction of **63a** produced butenolide **65** instead, the acetal group of which was presumably formed between the ketone and the 2′- and 3′-hydroxy groups of the intermediate triol **64**. It is notable that **65** has previously been isolated as an undesired side-product by other research teams during their syntheses of **7a**.[56,60e,60f,60g] Perhaps more interesting is the hitherto unknown conversion of **65** back to **7a**, which presumably also proceeds through **64** as the intermediate. Thus, by treatment with *p*TsOH in aqueous acetone, compound **65** was transformed in 52% yield to syringolide 1 (**7a**), the structure and absolute configuration of which were confirmed by an X-ray crystallographic study.[59] The specific rotation and other physical and spectroscopic data of **7a** and **7b**[59] are in full agreement with those of the natural[8][9] and synthetic[56][60] **7a** and **7b** reported in the literature.

Conclusion

In the foregoing discussion, it has been shown that 1,7-dioxaspiro[4.4]nonane and 1,7-dioxaspiro[4.4]non-8-ene skeletons may be obtained conveniently by means of an intramolecular conjugate addition methodology. In order to assess this synthetic design in a systematic manner, it was first used to convert hispanolone (**2**) to prehispanolone (**1**). The same avenue was subsequently explored by the construction of sphydrofuran (**3**), secosyrin 1 (**5a**), and secosyrin 2 (**5b**). Finally, an efficient synthesis of syringolide 1 (**7a**) and syringolide 2 (**7b**) was delineated. However, a more competent method allowing greater stereocontrol in the intramolecular conjugate addition is still lacking. Thus, the cyclization of **13** to give **14** (Scheme 2) as well as that of **36** to give **37** and **38** (Scheme 4) proceeds all with little stereocontrol, although in the cyclization of **52** to form **53** and **54** a 1:5 product ratio was observed (Scheme 7). The regioselective silylation of furans **8**, **34**, and **49** was also considered as a challenging undertaking. The novel deprotonation−silylation process described herein allows only a partial control of regioselectivity, but time-consuming chromatographic separations of starting materials from the resulting silylated



Scheme 12. Synthesis of syringolides **7a** and **7b**

products are required. Thus, future efforts will be directed towards a detailed mechanistic study in order to shed some light on the underlying causes of the currently disappointing regio- and stereoselectivities under consideration in this Microreview.

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