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# Synthesis of (+)-Manoalide via a Copper(I)-Mediated 1,2-Metalate Rearrangement

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An enantiospecific synthesis of the phospholipase $A_2$ inhibitor (+)-(4*R*)-manoalide is reported in which all 25 carbons of the sesterterpenoid skeleton are constructed from 3-furaldehyde, trimethylalane, oxirane, CO, $\beta$-ionone, and propargyl bromide. The overall yield for the longest linear sequence (12 steps) is 12%. Key steps include (a) a zirconium-catalyzed carboalumination reaction to construct the C10−C11 trisubstituted alkene, (b) a Cu(I)-mediated 1,2-metalate rearrangement to construct the C6−C7 trisubstituted alkene, (c) a Sharpless kinetic resolution to secure the (4*R*)-stereochemistry, (d) generation of a 5-stannyl-2,3-dihydrofuran by Mo-catalyzed cycloisomerization of a homopropargylic alcohol, and (e) construction of the hydroxyfuranone ring by photooxidation of a silylfuran.

## Introduction

In 1980 de Silva and Scheuer reported the isolation and structure determination of manoalide (**1**), a sesterterpenoid metabolite from the Pacific sponge *Luffariella variabilis*.[1] Owing to the presence of two hemiacetal moieties at C24 and C25, manoalide is a mixture of diastereoisomers that undergo easy ring-chain tautomerism to the dialdehyde **2**. The absolute stereochemistry of the single remaining nonfluxional stereogenic center at C4 was ascertained by correlation with a synthetic derivative.[2,3] The first total synthesis of racemic manoalide was reported in 1985 by Katsumura and co-workers,[4] and this was followed by six syntheses of the racemate[5−8] (including our own contribution[9]). However, the first enantiospecific synthesis of (+)-(4*R*)-manoalide evaded conquest until the concise asymmetric aldol approach of the Sodano group in 1999.[10] Syntheses of various pyranofuranone fragments have also been described.[11−14]

Manoalide is a potent and irreversible inhibitor of phospholipase $A_2$ ($PLA_2$), the hydrolytic enzyme that catalyses arachidonic acid release from membrane-bound phosphoglycerides leading to the formation of pro-inflammatory mediators such as the leukotrienes and prostaglandins.[15,16] Moreover, it also reduces the expression of COX-2.[17] Current opinion is that irreversible binding of manoalide to $PLA_2$ is the consequence of Schiff base formation between the aldehyde tautomer of the hydroxyfuranone ring of two manoalide molecules and two remote lysine residues on the interfacial recognition surface of the enzyme. Neither lysine is associated with the active site of the enzyme; hence some residual catalytic activity of the doubly bound enzyme is observed.[18] However, the $PLA_2$ inhibition by cacospongionolide E (**3**) suggests that Schiff base formation with the aldehyde tautomer derived from the hydroxypyran ring (C24) is not essential for biological activity.[19] Another dominant molecular feature that contributes to the potency and efficacy of manoalide is the presence of a large hydrophobic chain. Sodano and co-workers have

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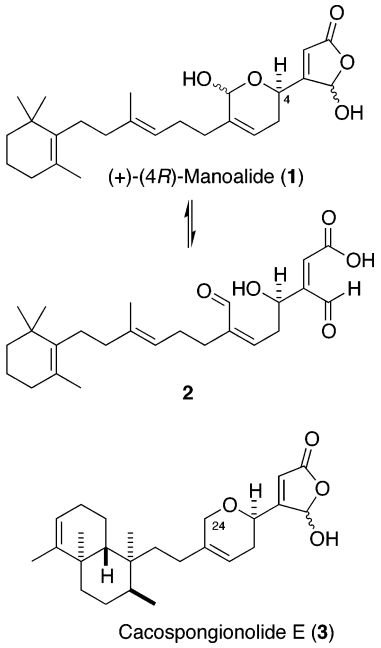
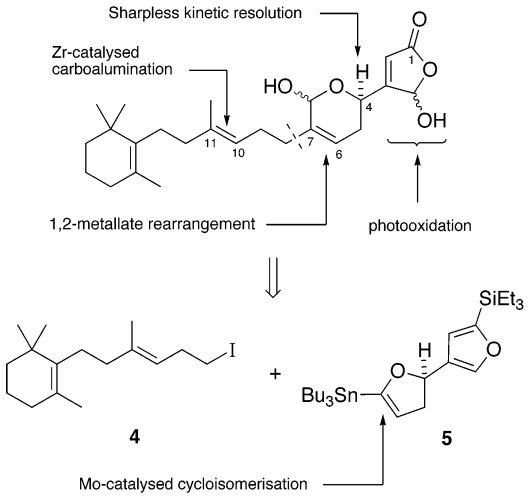



**FIGURE 1.**

**SCHEME 1. Disconnections and Key Steps**



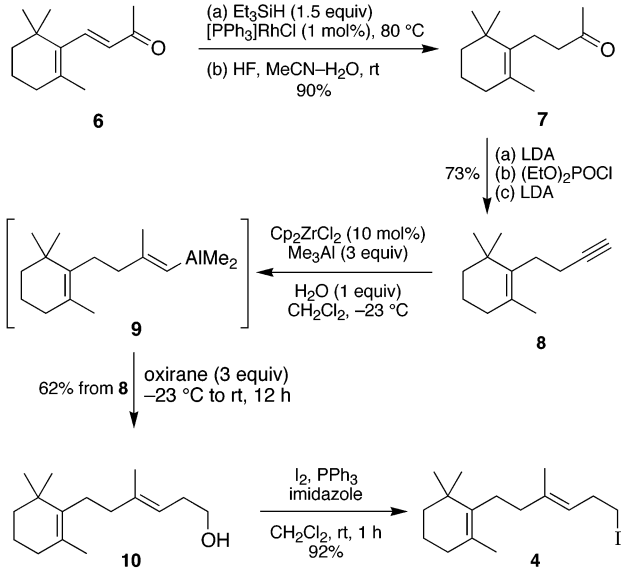

summarized the extensive biochemistry of manoalide and its many natural and unnatural relatives.[20]

## Results and Discussion

We now report a synthesis of (4*R*)-manoalide in which all 25 carbons are derived from 6 simple commercial fragments: 3-furaldehyde, trimethylalane, oxirane, CO, *β*-ionone, and propargyl bromide. The key steps together with the two principal fragments **4** and **5** encompassing 24 of the 25 carbons of the target are summarized in the synthetic map depicted in Scheme 1. The synthesis can be divided into 3 phases as described below.

**Phase 1: Synthesis of Iodoalkane 4.** Synthesis of iodoalkane **4** (Scheme 2) began with the conjugate reduction of *β*-ionone (**6**). One attractive and economic method based on the use of sodium dithionite in hot

**SCHEME 2. Synthesis of Iodoalkane 4**




aqueous toluene under phase transfer catalysis was examined in detail because it could be performed on a large scale.[7,21] However, the reaction did not go to completion despite the use of excess reagents and the dihydro-*β*-ionone (**7**) was invariably contaminated with 5−10% of unreacted starting material, which required tedious chromatography to separate. Far better is a mild procedure of Laube and co-workers[22] involving Rh-catalyzed conjugate hydrosilylation of *β*-ionone with triethylsilane followed by hydrolysis of the enol silane intermediate to give the dihydro-*β*-ionone in 90% yield. The reaction can be performed on large scale under solvent-free conditions and only 1 mol % of the commercial $[Ph_3P]_3RhCl$ catalyst is required. Moreover, the product is devoid of unreacted starting material.

Regioselective dehydration of dihydro-*β*-ionone via the enol phosphate derivative gave the terminal alkyne **8** in 73% yield for the 3-step sequence.[23] The known conversion of alkyne **8** to the homoallylic alcohol **10** benefited from two significant improvements. First, the Negishi carboalumination reaction generating the alkenyl dimethylalane intermediate **9** was conducted in the presence of 1 equiv of water as recommended by Wipf and co-workers[24] leading to a faster reaction and a reduction in the amount of zirconocene dichloride from 1 equiv to just 10 mol %. The second improvement entailed the direct reaction of the alkenyl dimethylalane **9** with oxirane to give the homoallylic alcohol **10** without the activation of the alane as the ate complex with BuLi as reported previously.[25,26] Although there was no improvement in overall yield in the conversion of **8** to **10** (62%), the experimental procedure was abbreviated and simpli-

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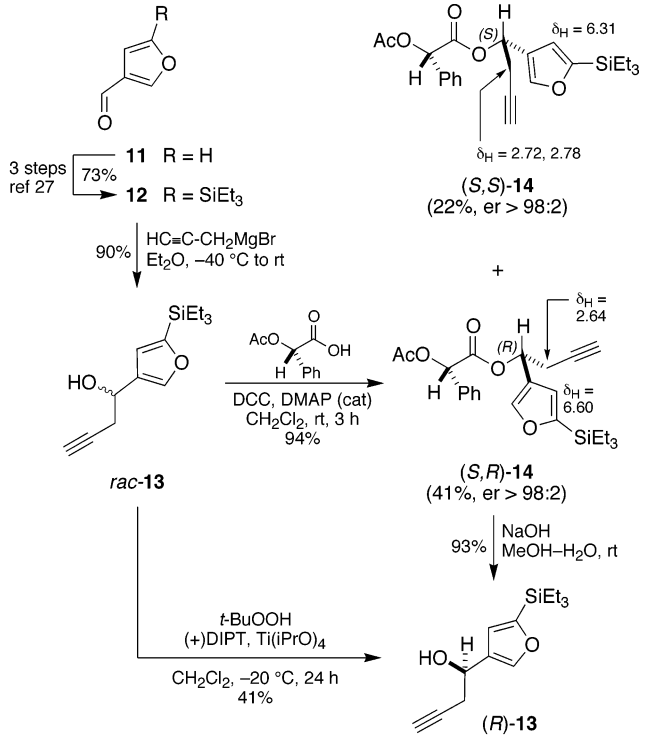
**SCHEME 3. Synthesis of Alcohol (*R*)-13 by Chromatographic and Kinetic Resolution**

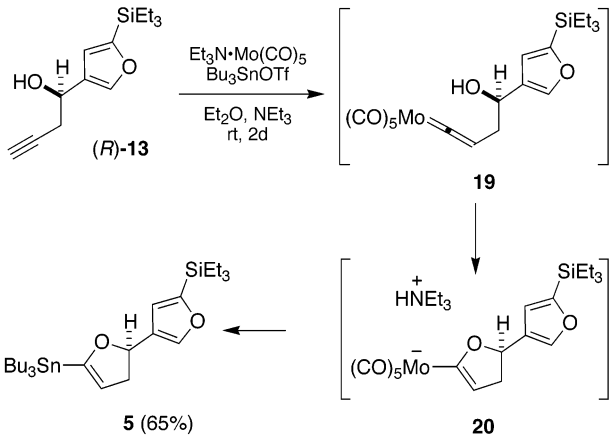



fied. Finally conversion of the alcohol **10** to iodoalkane **4** was accomplished in a single step (92%) with standard procedures. The overall yield for the 8-step sequence is 37%.

**Phase 2: Synthesis of the 2,3-Dihydro-[2,3′]-bifuranyl 5.** Synthesis of the second key intermediate in our synthesis, the 2,3-dihydro-[2,3′]-bifuranyl derivative **5**, entailed three operations: (1) appendage of the triethylsilyl group; (2) creation of the C4 (manoalide numbering) stereogenic center; and (3) construction of the 5-tributylstannyl-2,3-dihydrofuran ring. The sequence began with the appendage of a triethylsilyl group at C5 of 3-furaldehyde. The triethylsilyl group, which served the dual purpose of preventing metalation of the furan ring and activating the furan during a subsequent photooxidation, was installed by temporary protection of the aldehyde in 3-furaldehyde (**11**, Scheme 3) by nucleophilic addition of lithium morpholide to give an adduct that was then lithiated at the 5-position with *s*-BuLi. Addition of triethylsilyl chloride followed by aqueous workup returned the 5-triethylsilyl-3-furaldehyde **12** in 73% yield for the one-pot sequence.[27]

The synthesis of enantiomerically pure alcohol (*R*)-**13** by catalytic asymmetric methods (see below) was impractical and therefore abandoned in favor of resolution-based methods. Thus, the racemic alcohol *rac*-**13**, prepared by addition of propargylmagnesium bromide to aldehyde **12**, was esterified with (*S*)-*O*-acetyl-mandelic acid with use of DCC[28] (Scheme 3) and the mixture of diastereoisomeric esters was separated by column chromatography to give pure (*S*,*R*)-**14** (41%) and (*S*,*S*)-**14**

**SCHEME 4. Mo-Catalyzed CycloIsomerization of Alkynol (*R*)-13**




(22%). The configurations of the two diastereoisomers were assigned from the chemical shifts of the propargylic protons according to the Mosher−Trost model.[29,30] In the case of (*S*,*R*)-**14**, the propargylic protons at $\delta$ 2.64 were shielded by the phenyl group in the conformation depicted relative to the corresponding protons in the (*S*,*S*)-diastereoisomer ($\delta$ 2.72 and 2.78). Moreover, the mandelate proton in (*S*,*R*)-**14** at $\delta$ 6.22 was shielded by the furan ring whereas the corresponding proton in the (*S*,*S*)-diastereoisomer appeared at $\delta$ 6.52. Hydrolysis of the ester (*S*,*R*)-**14** gave the alcohol (*R*)-**13** in 93% yield with an er of 98:2. The chromatographic resolution strategy was able to deliver gram quantities of enantiopure (*R*)-**13** but the small difference in $R_f$ between the diastereoisomeric esters made the chromatographic separation difficult. A far more practical procedure, and the method of choice, was the kinetic resolution of *rac*-**13** under Sharpless asymmetric epoxidation conditions[31] whereupon the desired (*R*)-alcohol was isolated by an easy column chromatography in 41% yield.

Five methods for the asymmetric addition of allenylmetallic reagents to aldehyde **12** were evaluated. The yield and enantiomeric ratio (er) of the adducts (*R*)-**13** and (*S*)-**13** are summarized in Table 1. The lowest enantioselectivities were obtained in the addition of allenyl-/propargylzinc reagents with chiral ethanolamines **16** and **17** as chiral adjuvants (entries 2 and 3). The allenylboronate derived from the dibenzyl tartrate **15** added in good yield (71%) but the er (80:20) was unacceptable (entry 1).[32] By contrast the allenylboron reagent derived from **18** gave an acceptable er (91:9) but the yield was only modest at best (49%, entry 5).[33] Potentially the best of the asymmetric methods examined was that of Keck involving addition of an allenylstannane to aldehyde **12** under the aegis of an (*R*)-BINOL-modified

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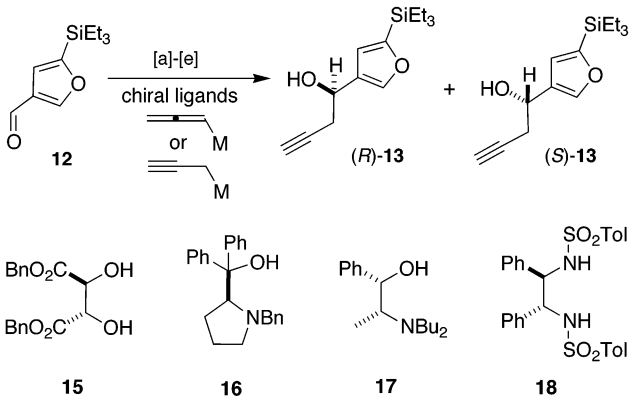
**TABLE 1. Asymmetric Propargylation of 5-(Triethylsilyl)-3-furaldehyde (12)**




| entry | reagents and conditions | yield (%) | er (*R*:*S*)[b] |
|---|---|---|---|
| 1 | [a]: $H_2C{=}C{=}CH{-}B(OH)_2$ (2.5 equiv), **15** (1.9 equiv), 5 Å MS, $CH_2Cl_2$, −78 °C, 3 d | 71 | 80:20 |
| 2 | [b]: $H_2C{=}C{=}CH{-}I/HC{\equiv}C{-}CH_2I$ (2:1, 2.2 equiv), $ZnEt_2$ (2.2 equiv), **16** (20 mol %), PhMe, 0 °C, 4 h | 80 | 30:70 |
| 3 | [c]: $H_2C{=}C{=}CH{-}I/HC{\equiv}C{-}CH_2I$ (2:1, 2.2 equiv), $ZnEt_2$ (2.2 equiv), **17** (20 mol %), PhMe, 0 °C, 4 h | 84 | 55:45 |
| 4 | [d]: $H_2C{=}C{=}CHSnBu_3$ (2.0 equiv), (*R*)-BINOL (25 mol %), $Ti(^iPrO)_4$ (25 mol %), 4 Å MS, $PrS{-}BEt_2$ (2.0 equiv), $CH_2Cl_2$, −20 °C, 10 d | 87[a] | 96:4 |
| 5 | [e]: **18** (1.1 equiv), $BBr_3$ (1.1 equiv), $CH_2Cl_2$, rt, 40 min; add $HC{\equiv}C{-}CH_2SnPh_3$, 0 °C, 40 min; add aldehyde, −78 °C, 4 h | 49 | 91:9 |

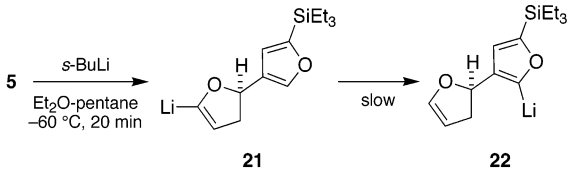
[a] Yield based on 40% recovered starting material. [b] The ratio and configuration was determined by $^1H$ NMR spectroscopy of the (*S*)-*O*-acetyl mandelate esters.

Lewis acid (entry 4).[34,35] The excellent enantiomeric ratio (96:4) and high yield (87% based on recovered starting material) was vitiated by the long reaction times (ca 10 days) at the low temperature required to achieve high er, the capriciousness of the reaction, and the failure of the reaction to go to completion.

The final hurdle in our synthesis of 2,3-dihydro-[2,3′]-bifuranyl **5** was the construction of the 5-tributylstannyl-2,3-dihydrofuran ring (Scheme 4), a task that was easily accomplished in a single step by the Mo-catalyzed cycloisomerization method of McDonald.[36] The method entailed the photochemical generation of $Et_3N{\cdot}Mo(CO)_5$ and its subsequent reaction with the alkynol (*R*)-**13** and $Bu_3SnOTf$ in the presence of excess $NEt_3$. After 48 h at room temperature, the acid-sensitive target **5** was isolated in 65% yield. A plausible mechanism for the transformation was proposed by McDonald:[37] reaction of the terminal alkyne in (*R*)-**13** with $Et_3N{\cdot}Mo(CO)_5$ results in formation of a Fischer-type vinylidenecarbene **19** that cyclizes under the reaction conditions to the dihydrofuran **20** whence reaction with $Bu_3SnOTf$ affords the product and regenerates the $Et_3N{\cdot}Mo(CO)_5$.

**Phase 3: Construction of the C6−C7 Trisubstituted Alkene.** The principal goals in the third and final phase of the synthesis were the union of fragments **4** and **5** (as their lithium derivatives) and the construction of the C6−C7 trisubstituted alkene. The aim in preparing the stannane **5** was to provide a route to the corresponding lithium reagent **21** (Scheme 5)—an essential ingredient in the 1,2-metalate rearrangement. The transmetalation of α-stannyl enol ethers with BuLi is well-documented as an easy and efficient reaction,[38] but in the case at hand, the desired lithium reagent **21** underwent competitive rearrangement to the more thermodynamically stable furanyllithium **22** under the transmetalation conditions with consequent complications in the next step (see below). However, the problem was minimized by accelerating the transmetalation step by using *s*-BuLi at −60 °C instead of *n*-BuLi and by using a mixture of $Et_2O$ and pentane as the solvent.

**SCHEME 5. Transmetalation of 5-Tributylstannyl-2,3-dihydrofuran 5**




A Cu(I)-mediated 1,2-metalate rearrangement that is the apex of our synthesis (Scheme 6)[39,40] was initiated by halogen−metal exchange of iodoalkane **4** with *t*-BuLi[41,42] to afford a homoallylic lithium derivative that was converted to a mixed cuprate **23** by reaction with 1-pentynylcopper. The resultant cuprate was then added to a solution of the lithiated dihydrofuran **21** at −78 °C to give a putative higher order cuprate **24** that underwent 1,2-metalate rearrangement on gradual warming to room temperature. The resultant higher order oxycuprate **25**

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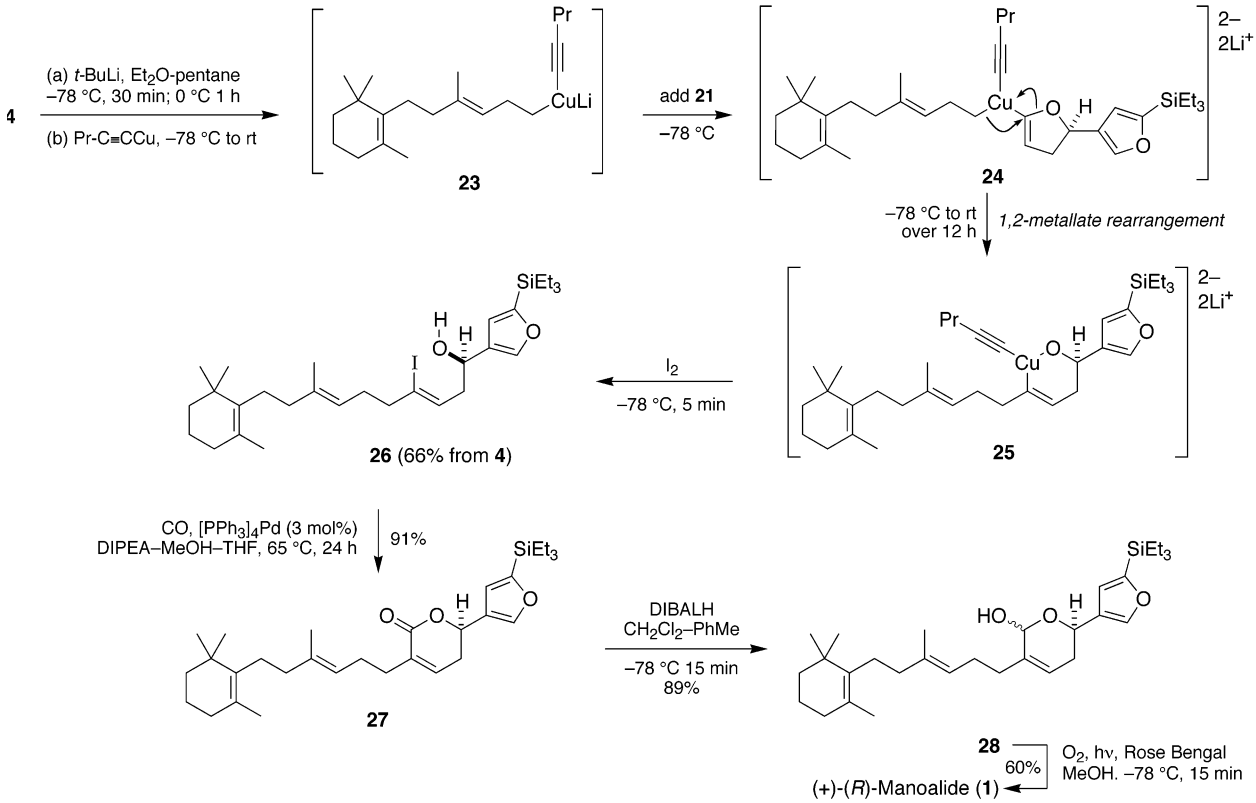
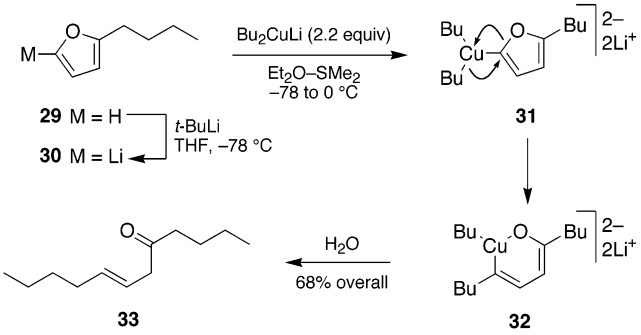
**SCHEME 6. The Key Step: A 1,2-Metalate Rearrangement**




was then quenched with iodine to give the trisubstituted iodoalkene **26** in 65% overall yield from stannane **5** and iodoalkane **4**. A similar sequence, in which CuCN was used instead of 1-pentynylcopper, gave the iodoalkene **26** in 58% overall yield. To install the last remaining carbon of the manoalide skeleton, the iodoalkene was subjected to a Pd(0)-catalyzed carbonylation[43] in which the intermediate acylpalladium(II) species was captured by reaction with the proximate hydroxyl group to give the lactone **27** in 91% yield. To complete the synthesis, the lactone was reduced to the corresponding lactol with DIBALH whereupon photooxidation of the silylfuran[44] generated the hydroxyfuranone of manoalide in 60% yield. The $^1$H NMR spectrum of the product was identical with the NMR spectrum of racemic manoalide kindly provided by Dr. Michael Garst and the sign and magnitude of the $[\alpha]_D$ (+77.5) was comparable to the value reported by Kobayashi and co-workers (+80.0).[3]

**2-Furyllithiums Undergo Cu(I)-Mediated 1,2-Metalate Rearrangment.** Above we alluded to complications arising from the rearrangement of the dihydrofuryllithium derivative **21** to the 2-furyllithium **22**. We suspected that **22** was participating in the 1,2-metalate rearrangement with the consequent destruction of the furan ring. Our suspicions were confirmed by the reaction of the simpler 5-butyl-2-furyllithium with $Bu_2CuLi$ to give the $\beta,\gamma$-unsaturated ketone **33** in 68% yield in accord with the mechanism shown in Scheme 7.[45]

**SCHEME 7. 1,2-Metalate Rearrangement of 5-Butyl-2-furyllithium**




## Conclusion

We have accomplished the synthesis of (+)-manoalide in 12% overall yield for the longest linear sequence of 12 steps from commercial starting materials (3-furaldehyde, trimethylalane, oxirane, CO, $\beta$-ionone, and propargyl bromide). Noteworthy features include (a) the discovery of conditions for transmetallating stannyldihydrofuran **5** without competing metalation of the furan, (b) the use of cyanide and pentyne as nontransferrable ligands in the key 1,2-metalate rearrangement step used to construct the C6−C7 trisubstituted double bond, and (c) the discovery that furan rings participate in Cu-mediated 1,2-metalate rearrangements. The weakest link in the synthesis was the 6-step sequence (18% overall) by which 3-furaldehyde was converted to the stannane **5** because

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(45) A related rearrangement involving furylzirconocene derivatives is known: Erker, G.; Petrenz, R.; Krüger, C.; Lutz, F.; Weiss, A.; Werner, S. *Organometallics* **1992**, *11*, 1646−1655.

of the inherent inefficiency in the resolution of the furylcarbinol *rac*-**13**.

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**Supporting Information Available:** Experimental details and characterization data for compounds **1**, **4**, **5**, **7**, **10**, (*R*)-**13**, (*S*,*R*)-**14**, (*S*,*S*)-**14**, **26**, **27**, **28**, and **33** together with details of the asymmetric propargylation of 5-triethylsilyl-3-furaldehyde (**12**); copies of $^1$H spectra for compounds **1**, **4**, **5**, **13**, **26**, **27**, **28,** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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