Regio- and Diastereoselective Allenylation of Aldehydes in Aqueous Media: Total Synthesis of (+)-Goniofufurone[1]

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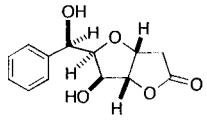
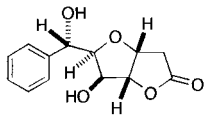
The regio- and diastereoselectivities of metal-mediated allenylation of carbonyl compounds were investigated in aqueous media. Different metal mediators showed varied regioselectivities on product formation during propargylation−allenylation reactions of carbonyl compounds with simple propargyl bromide. Under the standard reaction conditions, the use of indium provided the highest regioselectivity, with a preference of formation of the homopropargyl alcohol. The use of tin and bismuth as the metal mediator provided slightly lower selectivities with the same preference. The use of zinc and cadmium as the mediators further lowered the product selectivity. The reactions of an aliphatic aldehyde with simple propargyl bromide showed a lower selectivity than the reaction of an aromatic aldehyde in most cases, except for the use of tin or zinc (where comparable selectivities were observed). On the other hand, the reaction of terminal-substituted propargyl bromides with aldehydes mediated by indium showed a high regioselectivity in forming allenylation products. The indium-mediated allenylation of carbonyl compounds bearing an α-hydroxyl group also proceeded with a high diastereoselectivity, forming *syn*-diols predominantly in aqueous ethanol. The high diastereoselectivity in allenylation of α-hydroxyl-substituted aldehydes was attributed to the chelation effect exhibited by the α-hydroxyl substitutent. Through the use of this highly diastereoselective allenylation, (+)-goniofufurone was synthesized from D-glucurono-6,3-lactone.

Introduction

Carbohydrates have long been a source of scientific interest because of their abundance in nature, their wide range of biological activities, and the synthetic challenges posed by their polyhydroxylated structures.[2] Methods that could be used to transform and synthesize polyhydroxylated compounds in their underivatized states are particularly desirable. In this respect, the Kiliani−Fischer synthesis is the earliest carbohydrate chemical synthesis without the use of a protecting group.[3] The recent development of Barbier−Grignard-type carbon−carbon bond formations in aqueous media offers opportunities in the syntheses of various heavily oxygenated, biologically important agents.[4] Among the various biologically important, polyhydroxylated compounds are the ones recently isolated from the Asian trees of the genus *Goniothalamus*. These trees have long been recognized as a potential source of chemotherapeutic agents. The extracts and leaves of *Goniothalamus* have traditionally been used for the treatment of edema and rheumatism,[5] as a pain killer and a mosquito repellent,[6] and as an abortifacient.[7] From the constituents of these plants, McLaughlin discovered a number of novel styryl lactones which were found to possess moderate to significant cytotoxicities against several human tumors. Among the key components in the extracts are (+)-goniofufurone (**1**)[8] and (+)-7-*epi*-goniofufurone (**2**).[9] The



1 (+)-Goniofufurone



2 (+)-7-epi-Goniofufurone

absolute stereochemistry of (+)-goniofufurone was established by Shing through the total synthesis of *ent*-(−

(1) Presented at the 215th ACS National Meeting, Dallas, April 1998. Taken in part from; Yi, X.-H. Ph.D. Dissertation, Tulane University, 1998.

(2) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983.

(3) Webber, J. M. *Advances in Carbohydrate Chemistry*; Academic Press: New York, 1962; Vol. 17.

(4) For general reviews, see: Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. Li, C. J. *Tetrahedron* **1996**, *52*, 5643. Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. For applications of aqueous metal-mediated reactions in carbohydrate syntheses, see: Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 6674. Chan, T. H.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 747. Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937. Gao, J.; Harter, R.; Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 3714. Binder, W. H.; Prenner, R. H.; Schmid, W. *Tetrahedron* **1994**, *50*, 749. Chan, T. H.; Lee, M. C. *J. Org. Chem.* **1995**, *60*, 4228. Wang, R.; Lim, C. M.; Tan, C. H.; Lim, B. K.; Sim, K. Y.; Loh, T. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825. For accounts on Diels−Alder type reactions in aqueous media, see: Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59. Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219. For reviews on transition-metal-catalyzed reactions in aqueous media, see: Herman, W. A.; Kohlpainter, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. For an account on Lewis acid catalysis in aqueous medium, see: Kobayashi, S. *Synlett* **1994**, 689. Recently, various Lewis acids were found to catalyze aqueous Barbier-type reactions, see: Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457 and references therein.

(5) Wu, Y. C.; Duh, C. Y.; Chang, F. R.; Chang, G. Y.; Wang, S. K.; Chang, J. J.; McPhail, D. R.; McPhail, A. T.; Lee, K. H. *J. Nat. Prod.* **1991**, *54*, 1077.

(6) Talapatra, S. K.; Basu, D.; Deb, T.; Goswami, S.; Talapatra, B. *Indian J. Chem., Sect. B* **1985**, *24*, 29.

(7) Sam, T. W.; Yeu, C. S.; Matsjeh, S.; Gan, E. K.; Razak, D.; Mohamed, A. L. *Tetrahedron Lett.* **1987**, *28*, 2541.

(8) Fang, X. P.; Anderson, J. E.; Chang, C. J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1655.

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)-**1**.[10] Subsequently, several synthetic studies have been carried out on the synthesis of **1**.[11]

Our continued interests in metal-mediated carbon−carbon bond formation in aqueous media[12] led us to study (+)-goniofufurone and the related styryl compounds. Recently, we reported a highly regio- and diastereoselective indium-mediated allenylation of carbonyl compounds in aqueous media, which led to a concise total synthesis of (+)-goniofufurone from a readily available starting material.[13] Herein, we release our detailed study on this research.

Results and Discussion

During the assessment of the potential starting material for the desired target, a special feature of the 5−5 fused heterocyclic ring system attracted our attention. Such a structure is closely related to (+)-glucuronolactone, an inexpensive and readily available compound.[14] We could transform this 5−5 fused system into the target if we could find a method to regioselectively attach a benzyl alcohol unit to the hemiacetal carbon. For this aim, an allenylation of the hemiacetal followed by functional group transformations would generate the desired styryl derivative. In addition, it would require that the allenylation proceeds in a diastereoselective fashion, generating a diol derivative with a syn relationship. The initial assessment led us to derive the retrosynthetic analysis of (+)-goniofufurone via a metal-mediated allenylation reaction (Scheme 1).

Propargylation−Allenylation. As illustrated in the retrosynthetic analysis, the key connection of the proposed synthetic approach is the metal-mediated carbon−carbon bond formation between a carbonyl compound and a propargyl halide. To evaluate the feasibility of the proposed approach, we would be required to understand the regiochemistry of the connection (e.g., allenylation vs propargylation) and the diastereochemistry (syn vs anti).[15] In addition, other factors may also influence these selectivities. Thus, the initial regiochemistry of the carbon−carbon bond formation was investigated through the reaction between various aldehydes (**6**) and propargyl bromide (**7**) mediated by indium, zinc, tin, cadmium, and bismuth (eq 1). The results are compiled in Table 1. The

Scheme 1. Retrosynthetic Route to (+)-Goniofufurone

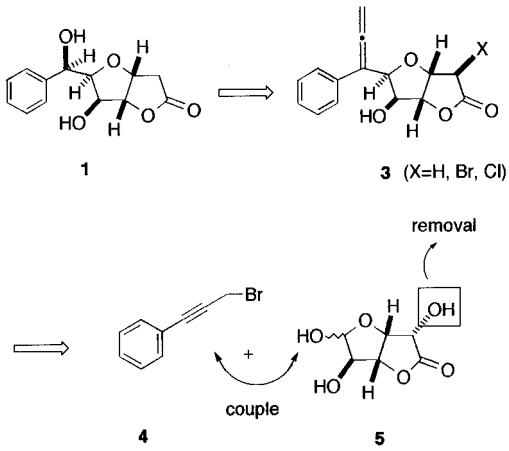
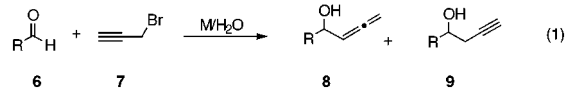


Table 1. Effect of Metals on the Propargylation−Allenylation Reaction[a]

entry	R	metal	**8**/**9**[b]	overall yield (%)
1	phenyl	In	1:6	72
2	*n*-hexyl	In	1:2	85
3	phenyl	Sn	1:5	60
4	*n*-hexyl	Sn	1:6[c]	60
5	phenyl	Zn	1:3	64
6	*n*-hexyl	Zn	1:4.4	65
7	phenyl	Bi	1:5	83
8	*n*-hexyl	Bi	1:1	60
9	phenyl	Cd	1:1	60
10	*n*-hexyl	Cd	1:1	20

[a] All reactions were carried out on 1 mmol scale at room temperature in H_2O/CH_3OH (2:1) with aldehyde/propargyl bromide/metal = 1:3:3. Yields were referred to as the nonoptimized, isolated ones after the column chromatography. [b] The ratio based on ^1H NMR. [c] The allenyl alcohol is isomerized to a conjugated ketone during isolation.



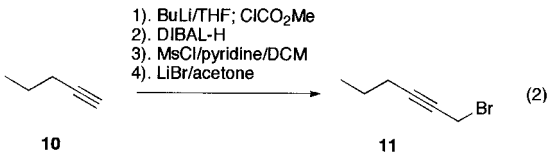
ratio of allenylation−propargylation (**8**/**9**) was determined by ^1H NMR measurement of peaks corresponding to the terminal alkyne and the internal olefin in the crude reaction mixture.

The reaction of propargyl bromide with benzaldehyde mediated by indium at room temperature in aqueous methanol was found to be fairly regioselective[16,17] with a preference for the formation of the homopropargyl alcohol. On the other hand, the same reaction mediated with tin[18] and bismuth[19] provided slightly lower selectivi-

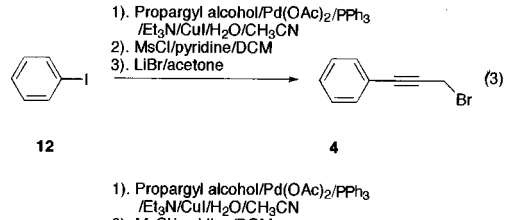
(9) Fang, X. P.; Anderson, J. E.; Chang, C. J.; McLaughlin, J. L.; Fanwick, P. E. *J. Nat. Prod.* **1991**, *54*, 1034.
(10) Shing, T. K. M.; Tsui, H. C. *J. Chem. Soc., Chem. Commun.* **1992**, 432.
(11) Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H. *J. Org. Chem.* **1995**, *60*, 3121 and references therein. Shing, T. K. M.; Tsui, H. C.; Zhou, Z. H. *J. Chem. Soc., Chem. Commun.* **1992**, 810. Murphy, P. J.; Dennison, S. T. *Tetrahedron* **1993**, *49*, 6695. Prakash, K. R. C.; Rao, S. P. *Tetrahedron* **1993**, *49*, 1505. Tsubuki, M.; Kanai, K.; Honda, T. *Synlett* **1993**, 653. Mukai, C.; Kim, I. J.; Hanaoka, M. *Tetrahedron Lett.* **1993**, *34*, 6081. Ye, J.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007. For more recent efforts in the synthesis of related compounds, see: Mereyala, H. B.; Reddy, R.; Krishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3567. Surivet, J.-P.; Vatele, J.-M. *Tetrahedron Lett.* **1997**, *38*, 819. Cagnolini, C.; Ferri, M.; Cox, B. *Tetrahedron* **1997**, *53*, 4815. Mukai, C.; Hirai, S.; Hanaoka, M. *Tetrahedron* **1996**, *52*, 6547.
(12) Li, C. J.; Chen, D. L.; Lu, Y. Q.; Haberman, J. X.; Mague, J. T. *Tetrahedron* **1998**, *54*, 2347. Li, C. J.; Meng, Y.; Yi, X. H.; Ma, J. H.; Chan, T. H. *J. Org. Chem.* **1997**, *62*, 8632. Haberman, J. X.; Li, C. J. *Tetrahedron Lett.* **1997**, *38*, 4735. Yi, X. H.; Meng, Y.; Li, C. J. *Tetrahedron Lett.* **1997**, *38*, 4731. Li, C. J.; Chen, D. L.; Lu, Y. Q.; Haberman, J. X.; Mague, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 4216. Lu, Y. Q.; Li, C. J. *Tetrahedron Lett.* **1996**, *37*, 471. Chen, D. L.; Li, C. J. *Tetrahedron Lett.* **1996**, *37*, 295. Li, C. J.; Lu, Y. Q. *Tetrahedron Lett.* **1995**, *36*, 2721. Li, C. J. *Tetrahedron Lett.* **1995**, *36*, 517.
(13) Yi, X. H.; Meng, Y.; Li, C. J. *Chem. Commun. (Cambridge)* **1998**, 449.
(14) Aldrich Chemical Co., 17.7 ¢/g.
(15) Preliminary studies were presented at the 213th ACS National Meeting, San Francisco, April 15, 1997.
(16) Isaac, M. B.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003. For an early example of allylation in aqueous media, see: Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. For early examples of indium reagents in organic solvents, see: Chao, L. C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. For more information on indium reagents, see: Cintas, P. *Synlett* **1995**, 1087. For the use of $InCl_3$(cat.)/M systems for aqueous Barbier-type reactions, see: Araki, S.; Jin, S. J.; Idou, Y.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736. Li, X. P.; Loh, T. P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535 and references therein.
(17) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500.
(18) For examples of allylation, see: Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. Wu, S. H.; Huang, B. Z.; Gao, X. *Synth. Commun.* **1990**, *20*, 1279.

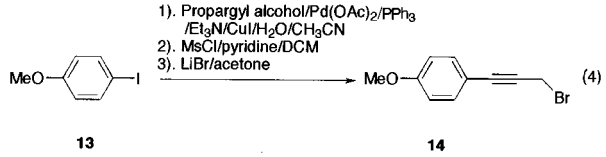
ties with the same preference. The reaction with zinc[20] further lowered the selectivity, and the use of cadmium had no selectivity on the product formation. The reactions of heptaldehyde with propargyl bromide in aqueous methanol mediated by indium, bismuth, or cadmium all gave low selectivity in the allenylation-propargylation. However, mediation by tin and zinc showed slightly higher selectivity favoring the propargylation product.

To study the regioselectivity of the reaction between aldehydes and propargyl bromides bearing different substituents, we prepared several bromo compounds. The compound **11** was readily prepared from 1-pentyne (**10**).

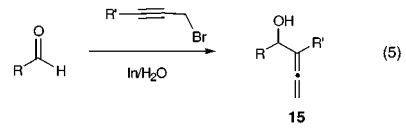


The starting material **10** was deprotonated with butyllithium and treated with methyl chloroformate; subsequent diisobutylaluminum hydride (DIBAL) reduction followed by mesylation and substitution (with lithium bromide) afforded the desired 1-bromo-2-hexyne (**11**) (eq 2). For the preparation of 3-bromo-1-propynylbenzene derivatives (eqs 3 and 4), iodobenzene (**12**) and 4-iodoanisole (**13**) were coupled with propargyl alcohol through a palladium-catalyzed reaction in an aqueous medium.[21]





Subsequent mesylation and bromination generated the desired bromides **4** and **14**. In contrast to the reaction of propargyl bromide itself, the reaction of propargyl bromides terminally substituted by an aliphatic or an aromatic substituent with aldehydes gave the allenylation products **15**, essentially as exclusive products (eq 5) (Table 2). During the present study, a similar high



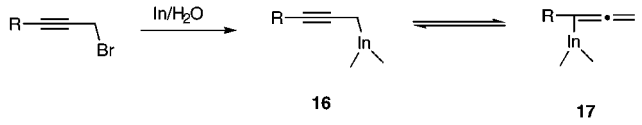
regioselectivity was also reported by Isaac and Chan in a more comprehensive investigation.[16] In agreement with the report by Isaac and Chan, the reaction of propargyl bromide with indium was proposed to generate an equilibrium between the allenylindium and propargylindium species in an aqueous medium (Scheme 2). Both intermediates can react with the carbonyl compounds, leading to carbon−carbon bond formation products. The selectivity was controlled by both steric and electronic effects.[16]

Table 2. Coupling of Aldehyde with Substituted Propargyl Bromides[a]

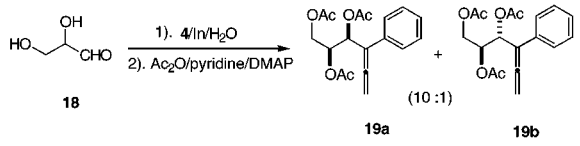
entry	R	R′	solvent	yield **15** (%)
1	phenyl	propyl	water	**15a** (69)
2	*n*-hexyl	phenyl	water	**15b** (53)
3	phenyl	*p*-MeO-phenyl	0.1 N HCl/95% ethanol	**15c** (77)
4	*n*-hexyl	*p*-MeO-phenyl	0.1 N HCl/95% ethanol	**15d** (50)
5	hydroxymethyl	phenyl	0.1 N HCl/95% ethanol	**15e** (57)

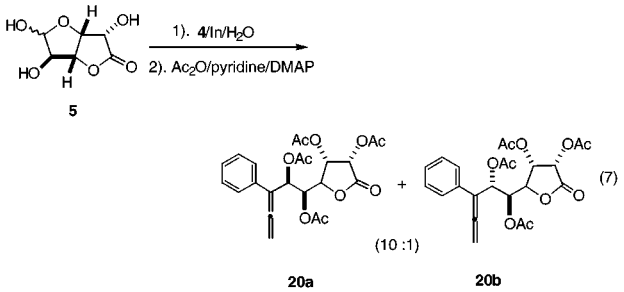
[a] All reactions were carried out in an air atmosphere. Yields were referred to as the isolated yields and were not optimized.

Scheme 2



The diastereoselectivity study was based on the results of the highly regioselective indium-mediated allenylation of aldehyde by substituent-bearing propargyl bromides. Coupling between 1-phenyl-3-bromopropyne and the α-hydroxyl substituted aldehydes **18** and **5** mediated by indium was investigated in aqueous ethanol (eqs 6 and 7). The use of aqueous alcohol as the reaction solvent





was desirable and provided a high diastereoselectivity. The corresponding allenylation products (after peracetylation: **19a** and **20a**) were obtained favoring the syn diastereomer. The high diastereoselectivity of this indium-mediated allenylation reaction can be attributed to a chelation control (Figure 1). The allene unit was primarily delivered from the least hindered face. A similar chelation-control model has been used exten-

(19) For allylation, see: Wada, M.; Ohki, H.; Akiba, K. Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738; *J. Chem. Soc., Chem. Commun.* **1987**, 708. Katritzky, A. R.; Shobana, N.; Harris, P. A. *Organometallics* **1992**, *11*, 1381. Minato, M.; Tsuji, J. *Chem. Lett.* **1988**, 2049.

(20) For early examples of allylation, see: Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. Wilson, S. R.; Guazzaaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.

(21) Calsalnuovo, A. L.; Calabreze, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324. Genet, P. J.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1995**, *31*, 348. Li, C. J.; Chen, D. L.; Costello, C. W. *Org. Process Res. Dev.* **1997**, *1*, 325. Li, C. J.; Slaven, W. T., IV; John, V. T.; Banerjee, S. *Chem. Commun. (London)* **1997**, 1569; Li, C. J.; Slaven, W. T., IV; Chen, Y. P.; John, V. T.; Rachakonda, S. H. *Chem. Commun. (Cambridge)* **1998**, 1351.

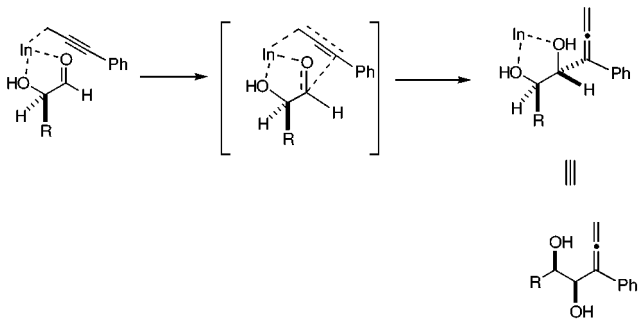


Figure 1.

sively, by Paquette and co-workers[22] in explaining the syn selectivity of aqueous allylation of carbonyl compounds.

Synthesis of (+)-Goniofufurone. The promising results of the regio- and diastereoselectivity studies led us to examine the synthesis of (+)-goniofufurone via the indium-mediated allenylation reaction. In our first approach (Scheme 3), the commercially available D-glucurono-6,3-lactone (**5**) was converted to **21** by treatment with a catalytic amount of toluenesulfonic acid in acetone in the presence of the hydroxyl group in the α position. Following a literature procedure,[23] the adduct **21** was then reacted with toluenesulfonic chloride in the presence of pyridine, yielding the corresponding tosylate **22**. The tosylate **22** was transformed to the bromide **23** (as a diastereomeric mixture) with lithium bromide in DMF solvent based on a literature procedure.[24] Attempts to effect a reductive elimination to generate the desired aldehyde compound **24** were not successful. Only the corresponding reduced product **25** was obtained.

To circumvent the problem associated with the reductive elimination, another synthetic route was designed. In this case, the key step was the allenylation between 3-bromo-1-propynylbenzene (**4**) and the α-reduced analogue of D-glucurono-6,3-lactone **27**. Low-temperature treatment of **21** with sulfuryl chloride yielded its α-chloro analogue **26** stereospecifically according to a literature procedure.[25] Then, reaction of **26** with zinc in saturated ammonium chloride solution mixed with tetrahydrofuran gave the reduced adduct **25** (in about 30% yield, although the reaction gave cleanly one product). The low isolated yield can be attributed to the high solubility of the accidentally deprotected adduct in water. Subsequent deprotection of the isopropylidene group produced the aqueous reaction substrate **27** quantitatively. After the aqueous indium-mediated allenylation, the crude material **28** was peracylated upon treatment with acetic anhydride along with pyridine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The peracetylated product **29** was isolated in 49% yield after flash column chromatography. However, problems were encountered during attempts to effect a base-catalyzed elimination. Instead of generating the desired α,β-unsaturated γ-lactone **30**, the reaction resulted in an unidentifiable mixture.

After careful examination of the problems during the first two approaches, we devised a third approach (Scheme 4). In this case, the starting material D-glucurono-6,3-lactone (**5**) was protected with an isopropylidene group following another literature procedure.[26] Replacement of toluenesulfonic acid with concentrated sulfuric acid enabled us to carry out the transformation into **21** without the use of cupric sulfate and to scale up the reaction. Following the same literature procedure,[26] **21** was converted into its corresponding triflate **31** by treatment with triflic anhydride in the presence of pyridine. Normally, a triflate is supposed to be reactive and unstable, but in this case, the product was kinetically stable enough to be stored at room temperature for a long period. After being stirred with lithium bromide at room temperature for 1 h, the triflate **31** was smoothly transformed into the desired diastereomer of the correponding bromo analogue **23** stereospecifically. The stereoconfiguration of the bromo at the α position of the lactone is crucial for the reductive elimination at a later stage. Treatment of **23** with trifluoroacetic acid and water[26] at room temperature cleanly afforded the desired substrate **32** in almost quantitative yield. Initial attempts to carry out the deprotection of the isopropylidene group by heating **23** with Dowex-50w appeared less satisfactory. Then, reaction of **32** with 3-bromo-1-propynylbenzene under the conditions of indium mediation in aqueous ethanol generated a mixture of allenylation products (56% yield) in which the desired allene compound **33** was the major component together with debromination and reductive elimination products. Again, the allenylation reaction showed a very high diastereoselectivity (>10:1) favoring the syn diastereomer. Subsequent ozonolysis of the allene compound **33** in methanol followed by a diastereoselective reduction with sodium borohydride[27] generated the desired alcohol as the predominant product (de = 3:1). The stereo configuration was assigned after the target compound was synthesized. To effect a reductive elimination, the crude polyol mixture was directly treated with concentrated sulfuric acid in acetic anhydride[28] to afford the peracetylation product **34** (calculated 75% yield from **33**), which showed decomposition on silica gel. Subsequent treatment of the peracetylation product **34** with sodium bisulfite/sodium sulfite[29] in aqueous methanol cleanly afforded the desired α,β-unsaturated γ-lactone, as shown by the ^{1}H NMR measurement of the crude product. To remove the acetyl protecting groups, the product was stirred in methanolic HCl for 2 days. Surprisingly, the reaction resulted in the deprotected product, which then cyclized, in situ, providing the target (+)-goniofufurone (**1**) in 44% yield. The spectroscopic data, the R_f value, and the melting point of the compound are consistent with the reports of (+)-goniofufurone in the literature.[11]

(22) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863. Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem. Soc.* **1997**, *62*, 4293. Bernardelli, P.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 8284. Marshall, J. A. *Chemtracts: Org. Chem.* **1997**, *10*, 481. Paquette, L. A.; Bennett, G. D.; Isaac, M. B.; Chhatriwalla, A. *J. Org. Chem.* **1998**, *63*, 1836.

(23) Hall, L. D.; Hough, L.; Pritchard, R. A. *J. Am. Chem. Soc.* **1961**, *83*, 1953.

(24) Irimajiri, T.; Yoshida, H.; Ogata, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3242.

(25) Parolis, H. *Carbohydr. Res.* **1983**, *114*, 21.

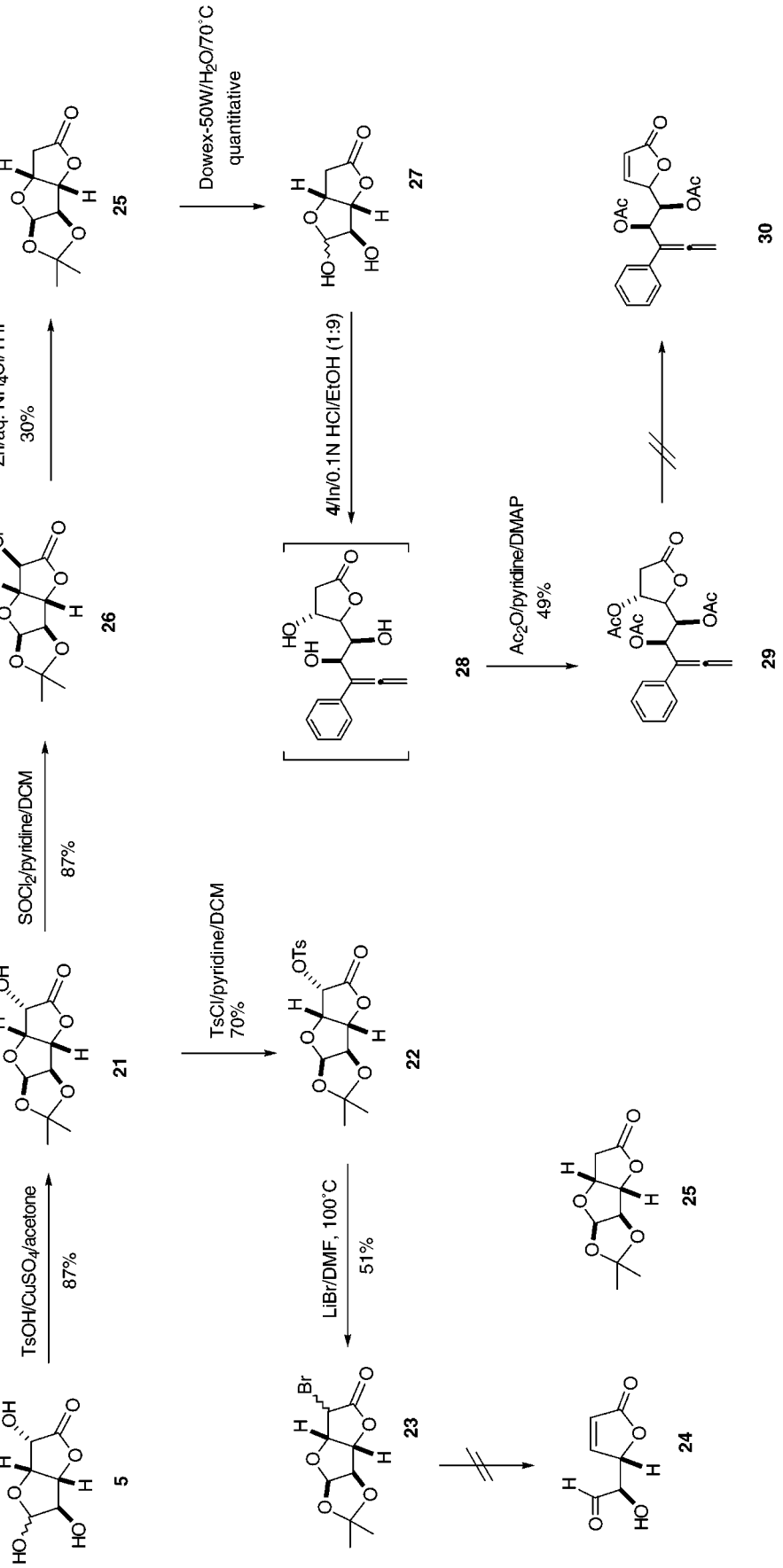
(26) Bashyal, B. P.; Chow, H.-K.; Fellow, L. E.; Fleet, G. W. J. *Tetrahedron* **1987**, *43*, 415.

(27) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York, 1991.

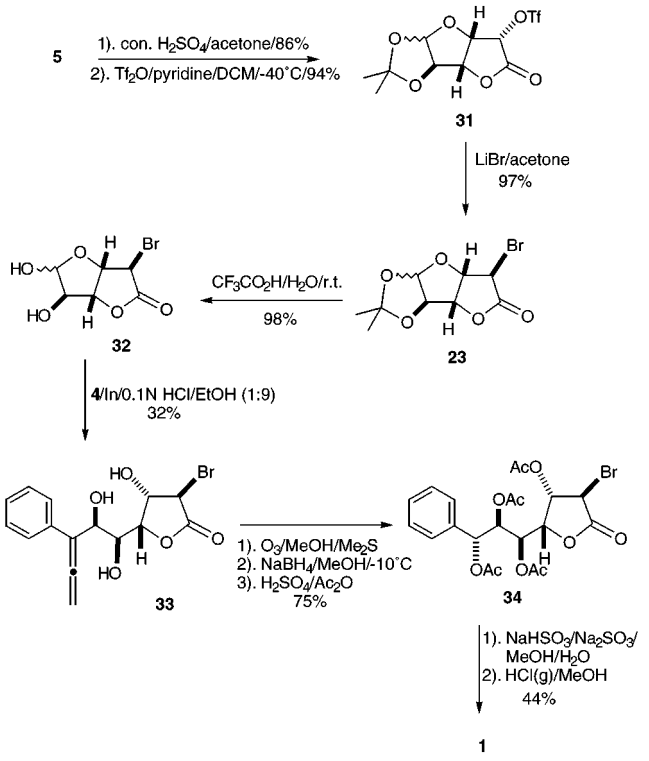
(28) Abdel-Akher, M.; Hamilton, J. K.; Smith, F. *J. Am. Chem. Soc.* **1951**, *73*, 4691.

(29) Vekemans, J. A. M.; Franken, G. A. M.; Dapperens, C. W. M.; Godefroi, E. F.; Chittenden, G. J. F. *J. Org. Chem.* **1988**, *53*, 627.

Scheme 3


TsOH/CuSO4/acetone
87%
SOCl2/pyridine/DCM
87%
Zn/aq. NH4Cl/THF
30%
Dowex-50W/H2O/70°C
quantitative
TsCl/pyridine/DCM
70%
LiBr/DMF, 100°C
51%
4/In/0.1N HCl/EtOH (1:9)
Ac2O/pyridine/DMAP
49%
5
21
22
23
24
25
26
27
28
29
30

Scheme 4. Synthesis of (+)-Goniofufurone



Conclusion

In conclusion, different metal mediators show varied regioselectivities on the product formation of propargylation−allenylation reaction of carbonyl compounds with propargyl bromide in aqueous media. The reaction of terminal-substituted propargyl bromides with aldehydes showed a high regioselectivity in forming allenylation products. The allenylation of carbonyl compounds bearing an α-hydroxyl group proceeded with a high diastereoselectivity predominantly forming *syn*-diols. The selectivity is attributed to chelation control. Through the use of this highly diastereoselective allenylation, a total synthesis of (+)-goniofufurone was completed. The scope and applications of this highly regio- and diastereoselective allenylation reaction to the syntheses of other polyhydroxylated compounds are presently under investigation.

Experimental Section

Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification. All organic solvents were freshly distilled prior to use. Air-sensitive reactions were generally conducted under a positive pressure of dry N_2 within glassware which had been oven-dried. Anhydrous solvents were obtained by distillation from the indicated drying agents: tetrahydrofuran (sodium, benzophenone ketyl) and methylene chloride (calcium hydride). Flash chromatography employed silica gel (40 μm). Mass spectra were obtained at the Center of Instrumental Facility of Tulane University and at the Biomedical Mass Spectrometry Unit of Medical School of McGill University. Elemental analyses were performed at the Center of Instrumental Facility of Tulane University.

General Procedure for the Effect of Metals on the Propargylation−Allenylation Reaction. To a suspension of benzaldehyde (106 mg, 1 mmol) in 10 mL of H_2O/CH_3OH (2:1) was added indium powder and **7** (228 mg, 2 mmol). The reaction mixture was stirred vigorously for 12 h, diluted with 1 N NH_4Cl, and extracted with ether (4 × 10 mL). The combined ethereal solution was dried over $MgSO_4$ and concentrated. Measurement of the **8**/**9** ratio was then taken. The propargylation and allenylation products (105 mg, 72%) were isolated by column chromatography on silica gel (eluent: hexane/ethyl acetate).

3-Bromo-1-propynylbenzene (4). A solution of iodobenzene (4.08 g, 20 mmol), propargyl alcohol (1.8 mL, 31 mmol), triethylamine (7 mL, 50 mmol), triphenylphosphine (270 mg, 1.03 mmol), palladium acetate (117 mg, 0.52 mmol), acetonitrile (30 mL), and water (15 mL) was stirred at room temperature under nitrogen overnight.[30] After filtration through Celite, most of the acetonitrile was evaporated, and the resulting suspension was extracted with ether (50 mL, 30 mL, 30 mL), washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated to give a crude oil, which was then purified by flash chromatography (70% methylene chloride in hexanes) to give 3-phenyl-2-propyn-1-ol[31] (1.47 g, 55% yield).

To a solution of the above product (1.47 g, 11.1 mmol) and triethylamine (2.4 mL, 17.3 mmol) in methylene chloride (25 mL) cooled to 0 °C was slowly added methanesulfonic chloride (1 mL, 13 mmol) over methylene chloride (10 mL). After being stirred for 30 min, the reaction mixture was washed with cold water, cold 5% hydrochloric acid, saturated sodium bicarbonate solution, and brine. After being dried over magnesium sulfate and filtered, the solution was concentrated to give a crude material.

A solution of the above crude material and lithium bromide (7.05 g, 81 mmol) in acetone (120 mL) was stoppered and stirred at room temperature overnight. After evaporation of acetone, the residue was dissolved in ether (100 mL), washed with water (3 × 30 mL) and brine, dried over magnesium sulfate, and filtered. The solution was concentrated to give the crude product, which was filtered through a pad of silica gel to produce **4**[32] (1.65 g, quantitative). IR (film): 1203, 1271, 1442, 1491, 1597, 2220 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 4.16 (2H, s), 7.28−7.40 (3H, m), 7.40−7.50 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 131.95, 128.97, 128.43, 122.17, 86.80, 84.39, 15.53. The compound was used directly in the coupling study.

1-Bromo-2-hexyne (11). To a solution of 1-pentyne (**10**, 1.0 mL, 10.2 mmol) in anhydrous tetrahydrofuran (20 mL) cooled to −78 °C under nitrogen was added dropwise a 1.6 M solution of butyllithium (6.3 mL, 10.1 mmol). After being stirred at the same temperature for 40 min, methyl chloroformate (0.8 mL, 10.4 mmol) in tetrahydrofuran (7 mL) was slowly added. The reaction mixture was stirred at −78 °C for 4 h before being warmed to room temperature. After evaporation of tetrahydrofuran under vacuum, the residue was dissolved in ether (20 mL) and washed with water (3 × 20 mL) and brine. After drying over magnesium sulfate, the solution was filtered and concentrated to provide methyl 2-hexynoate[33] (1.05 g, 83% yield). The compound was used directly for the next step without further purification.

To a solution of the above product (747 mg, 5.9 mmol) in anhydrous ether (20 mL) cooled to −78 °C under nitrogen was added diisobutylaluminum hydride (8.2 mL, 12.4 mmol) dropwise. After being stirred at −78 °C for 2 h, the reaction mixture was warmed to room temperature, and methanol (8 mL) was added; the solution turned into a gel. After being diluted with ether (30 mL), the mixture was stirred with potassium sodium tartrate (30 mL) for 1.5 h before the gel disappeared. After separation, the aqueous layer was extracted with ether (2 × 10 mL). The combined ethereal solution was washed with brine and dried over magnesium

(30) Claesson, A.; Sahlberg, C. *Tetrahedron* **1982**, *38*, 363.
(31) Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775.
(32) Padwa, A.; Rodriguez, A.; Tohidi, M.; Fukunaga, T. *J. Am. Chem. Soc.* **1983**, *105*, 933.
(33) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

sulfate. Subsequent filtration and removal of solvent furnished 2-hexyn-1-ol[34] (590 mg, 89% yield).

To a solution of the above crude product (496 mg, 5.06 mmol) and triethylamine (1.05 mL, 7.45 mmol) in methylene chloride (25 mL) cooled to 0 °C was slowly added methanesulfonyl chloride (0.45 mL, 5.83 mmol) over methylene chloride (5 mL) under nitrogen. After being stirred at 0 °C for 1 h, the solution was washed successively with cold water (20 mL), 5% cold hydrochloric acid (25 mL), cold water (20 mL), a saturated sodium bicarbonate solution (20 mL), and brine. After drying over magnesium sulfate, the solution was filtered and concentrated to give 2-hexyn-1-yl methanesulfonate[35] (717 mg, 80% yield).

A solution of the above crude product (698 mg, 3.97 mmol) and anhydrous lithium bromide (3.50 g, 40.2 mmol) in acetone (50 mL) was stirred at room temperature under nitrogen overnight. After vacuum filtration through Celite and evaporation of acetone, the residue was dissolved in ether (60 mL) and washed with water (50 mL, 20 mL, 20 mL) and brine. After being dried over magnesium sulfate and filtered, the solvent was removed, thus providing crude 1-bromo-2-hexyne (**11**),[36] which was purified by column chromatography on silica gel (eluent: 5% ethyl acetate in hexane) (296 mg, 46% yield). IR (film): 1209, 2234 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 0.98 (t, J = 7.4 Hz, 3H), 1.48−1.59 (m, 2H), 2.22 (tt, J = 7.0, 2.3 Hz, 2H), 3.93 (t, J = 2.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 88.04, 75.40, 21.83, 20.89, 15.77, 13.42.

1-(3-Bromo-1-propynyl)-4-methoxylbenzene (14). A mixture of 4-iodoanisole (20 g, 85.5 mmol), propargyl alcohol (14.36 g, 14.9 mL, 256.15 mmol), triethylamine (25.89 g, 35.66 mL, 255.86 mmol), triphenylphosphine (1.1207 g, 4.27 mmol), palladium acetate (479 mg, 2.13 mmol), copper(I) iodide (814 mg, 4.27 mmol), acetonitrile (210 mL), and water (40 mL) was stirred at room temperature under nitrogen for 29 h. After evaporation of the bulk of acetonitrile, the resulting suspension was extracted with ether (200 mL, 100 mL, 100 mL). The ethereal solution was washed with brine, dried over magnesium sulfate, and filtered. After evaporation of the solvent, the crude material was purified by column chromatography on silica gel (eluent: 17% ethyl acetate in hexane) to afford 3-(4-methoxyphenyl)-2-propyn-1-ol[37] (12.83 g, 93%).

A solution of 3-(4-methoxyphenyl)-2-propyn-1-ol (8.28 g, 51.1 mmol), triphenylphosphine (16.08 g, 61.3 mmol), and carbon tetrabromide (20.33 g, 61.3 mmol) in methylene chloride (150 mL) was stoppered and stirred at room temperature overnight. The solvent was evaporated to give the crude material. Column chromatography purification on silica gel (eluent: 9% ethyl acetate in hexane) gave 1-(3-bromo-1-propynyl)-4-methoxybenzene (**14**)[38] (8.37 g, 73%). IR (film): 2220, 1606, 1512, 1465 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.38 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 9.1, 2H), 4.17 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 160.05, 133.45, 114.14, 113.98, 86.94, 83.03, 55.32, 16.01.

3-(1-Phenyl-1-hydroxymethyl)-1,2-hexadiene (15a). A mixture of 1-bromo-2-hexyne (276 mg, 1.71 mmol), benzaldehyde (261.1 mg, 2.46 mmol), and indium (350 mg, 3.0 mmol) in water (2.2 mL) was stoppered and stirred vigorously at room temperature for 2 days. After being stirred with 0.1 N HCl (4.0 mL) for 1 h, the solution was extracted with ether (3 × 20 mL). The ethereal solution was washed with saturated sodium bicarbonate aqueous solution (2 × 20 mL) and brine, dried over magnesium sulfate, and filtered. After evaporation of the solvent, the crude material was purified by column chromatography on silica gel (eluent: 8% ether and 1% triethylamine in hexane) to give the title compound (**15a**)[39] (224 mg, 69%).

3-Phenyl-1,2-decadien-4-ol (15b). A suspension of heptaldehyde (228 mg, 2.0 mmol), 3-bromo-1-propynylbenzene (754 mg, 3.87 mmol), and indium (520 mg, 4.52 mmol) in water (10 mL) was stirred at room temperature overnight. After treatment with 2% hydrochloric acid (30 mL), the reaction mixture was extracted with ether. The ethereal solution was washed with water, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, and filtered. The solution was concentrated to give a crude product, which was purified with flash chromatography on silica gel to produce **15b** (245 mg, 53%). IR (film): 3390, 1940 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 0.90 (t, J = 6.7 Hz, 3H), 1.20−1.58 (m, 8H), 1.58−1.82 (m, 2H), 2.05−2.25 (br, 1H), 4.60−4.67 (m, 1H), 5.19−5.27 (m, 2H), 7.20−7.27 (m, 1H), 7.35 (t, J = 7.9 Hz, 2H), 7.47 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 14.1, 22.5, 25.8, 29.3, 31.8, 36.4, 70.0, 80.4, 110.0, 126.8, 128.6, 131.7, 134.8, 207.2. Anal. Calcd for $C_{13}H_{18}O$: C, 83.43; H, 9.63. Found: C, 83.17; H, 9.69.

3-(4-Methoxyphenyl)-4-phenyl-1,2-butadien-4-ol (15c). A solution of 1-(3-bromo-1-propynyl)-4-methoxybenzene (225 mg, 1 mmol), benzaldehyde (318 mg, 3 mmol), and indium powder (402 mg, 3.5 mmol) in 0.1 N aqueous HCl/95% ethanol (1:9; 6 mL) was stoppered and stirred at room temperature overnight. After evaporation of the ethanol, the mixture was extracted with ethyl ether (2 × 30 mL). The combined organic phase was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and filtered. After evaporation of the solvent, the crude material was purified by column chromatography on silica gel (eluent: 17% ethyl acetate in hexane) to afford 3-(4-methoxyphenyl)-4-phenyl-1,2-butadien-4-ol (**15c**) (195 mg, 77%). IR (film): 3410, 1940 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.46 (d, J = 7.7 Hz, 2H), 7.26−7.37 (m, 5H), 6.81 (d, J = 8.4 Hz, 2H), 5.68 (s, 1H), 5.20−5.30 (m, 2H), 3.75 (s, 3H), 2.40−2.60 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 55.2, 72.5, 81.3, 109.4, 113.9, 126.1, 127.0, 127.8, 128.1, 128.4, 142.1, 158.7, 207.4. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.72; H, 6.50.

3-(4-Methoxyphenyl)-1,2-decadien-4-ol (15d). A mixture of heptaldehyde (114 mg, 1 mmol), 1-(3-bromo-1-propynyl)-4-methoxybenzene (674.7 mg, 3 mmol), and indium powder (402 mg, 3.5 mmol) in 0.1 N aqueous HCl/95% ethanol (1:9) (6 mL) was stoppered and stirred at room temperature overnight. After evaporation of the ethanol, the mixture was extracted with ethyl ether (2 × 30 mL). The combined organic phase was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and filtered. After evaporation of the solvent, the crude material was purified by column chromatography on silica gel (eluent: 9% ethyl acetate in hexane) to afford 3-(4-methoxyphenyl)-1,2-decadien-4-ol (**15d**, 130 mg, 50%). IR (film): 3440, 1940 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.37 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 88 Hz, 2H), 5.20 (s, 2H), 4.54−4.60 (m, 1H), 3.80 (s, 3H), 1.8−1.9 (br, 1H), 1.2−1.8 (m, 10H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR(100 MHz, $CDCl_3$, ppm): δ 14.1, 22.6, 25.8, 29.2, 31.8, 36.2, 55.3, 69.9, 80.6, 109.5, 114.0, 126.7, 127.9, 158.7, 206.7. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.24; H, 9.38.

3-Phenyl-3,4-pentadiene-1,2-diol (15e). A solution of 2-butene-1,4-diol (1.28 g, 14.5 mmol) in methanol was cooled to −78 °C and bubbled with ozone until the solution turned blue. Subsequently, the excess ozone was flushed out with oxygen. After sodium bisulfite (9.16 g) was added, the suspension was allowed to warm to room temperature slowly and stirred overnight. Subsequent filtration provided a crude oil (1.02 g, 58%).

A suspension of the above product (120 mg, 2.0 mmol), 3-bromo-1-propynylbenzene (1.16 g, 6.0 mmol), and indium (465 mg, 4.0 mmol) in 0.1 N hydrochloric acid/ethanol (1:9, 12 mL) was stoppered and stirred at room temperature overnight. After being diluted with methanol (50 mL), the reaction

(34) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459.
(35) Hall, S. E.; Han, W. C.; Haslanger, M. F.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1986**, *29*, 2335.
(36) Couffignal, R.; Gaudemar, M.; Perriot, P. *Bull. Soc. Chim. Fr.* **1967**, *10*, 3909.
(37) Wadsworth, D. H.; Geer, S. M.; Detty, M. R. *J. Org. Chem.* **1987**, *52*, 3662.
(38) Wrobel, J. E.; Li, Z.; Dietrich, A. J. (American Home Products Corp.). PCT Int. Appl. WO95 24, 400(Cl. C07D277/36), Sept 14, 1995; U.S. Appl. 207,980, Mar 8 1994; 51 pp.
(39) Kulkarni, S. V.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4125.

mixture was neutralized with a 6 N aqueous sodium hydroxide solution and filtered through Celite under vacuum. Removal of solvent provided a crude product, which was purified by flash chromatography (eluent: 40% ethyl acetate in hexane) to give **15e** (202 mg, 57%). IR (film): 3250, 1940 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6, ppm): δ 3.60−3.76 (m, 2H), 4.00 (t, J = 5.8 Hz, 1H), 4.35 (d, J = 5.6 Hz, 1H), 4.64−4.72 (m, 1H), 5.18 (d, J = 2.0 Hz, 2H), 7.17−7.23 (m, 1H), 7.28−7.35 (m, 2H), 7.47−7.52 (m, 2H). ^{13}C NMR (100 MHz, acetone-d_6, ppm): δ 65.5, 70.3, 79.2, 106.6, 126.7, 128.4, 132, 135.3, 208.1. HRMS Calcd for $C_{11}H_{11}O$ (M + H − H_2O): 159.0810; found, 159.0810.

1,2,3-Tri-*O*-acetyl-4-phenyl-*erythro*-hexa-4,5-diene (19a). A suspension of glyceraldehyde (100 mg, 1.11 mmol), 3-bromo-1-propynylbenzene (550 mg, 2.82 mmol), and indium (260 mg, 2.26 mmol) in 0.1 N hydrochloric acid/ethanol (1:9; 5 mL) was stirred at room temperature for 6 h. Vacuum filtration provided a crude product, which was stirred with anhydrous triethylamine (20 mL, 144 mmol), 4-(dimethylamino)pyridine (7.5 mg), and acetic anhydride (2 mL, 20 mmol) overnight. Subsequent purification by flash chromatography on silica gel (eluent: 15% ethyl acetate in hexane) produced **19a** (210 mg, 63% yield). IR (film): 1940, 1740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.91 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 4.06 (dd, J = 12.0, 5.5 Hz, 1H), 4.27 (dd, J = 12.0, 3.2 Hz, 1H), 5.21 (s, 2H), 5.34−5.42 (m, 1H), 5.95 (d, J = 7.4 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 20.5, 20.7, 20.9, 62.5, 70.5, 71.5, 80.5, 103.7, 126.8, 127.6, 128.6, 131.6, 133.4, 169.9, 170.0, 170.3, 209.3. HRMS Calcd for $C_{18}H_{21}O_6$ (M + H); 333.1338; found, 333.1339.

2,3,5,6-Tetra-*O*-acetyl-7,8,9-trideoxy-7-phenyl-D-*glycero*-L-*gulo*-nona-7,8-dienoic Acid, 1,4-Lactone (20a). A suspension of D-glucurono-6,3-lactone (90 mg, 0.51 mmol), 3-bromo-1-propynylbenzene (390 mg, 2.0 mmol), and indium (202 mg, 1.76 mmol) in 0.1 N hydrochloric acid/ethanol (1:9; 10 mL) was stirred vigorously at room temperature overnight. After removal of solvent under vacuum, the residue was mixed with 4-(dimethylamino)pyridine (6.8 mg), acetic anhydride (6 mL, 60 mmol), and pyridine (20 mL, 259 mmol). The mixture was stirred at room temperature under nitrogen overnight before solvent was removed. Filtration of the reaction mixture through silica gel gave the crude product, which was then purified by flash chromatography to afford **20a** (148 mg, 63% yield). IR (film): 1940, 1820, 1750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.93 (s, 3H), 2.00 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 4.76−4.82 (m, 1H), 5.13−5.22 (m, 2H), 5.57 (dd, J = 7.7, 3.6 Hz, 1H), 5.66−5.71 (m, 3H), 7.19−7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 20.0, 20.1, 20.5, 20.7, 67.9, 69.0, 69.2, 69.7, 76.4, 80.4, 103.6, 127.0, 127.9, 128.8, 133.3, 166.3, 169.0, 169.1, 169.2, 169.5, 208.3. HRMS Calcd for $C_{23}H_{25}O_{10}$ (M + H): 461.1448; found, 461.1449.

5-Deoxy-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (25). A suspension of **26** (0.9925 g, 4.24 mmol) and zinc (2.70 g, 41.5 mmol) in a mixed-solvent system of tetrahydrofuran/aqueous saturated ammonium chloride (1:1; 30 mL) was stirred overnight. After evaporation of tetrahydrofuran, the mixture was extracted with methylene chloride (3 × 30 mL). The organic solution was washed with brine, dried over sodium sulfate, and filtered. Subsequent filtration through silica gel provided **25**[40] (250 mg, 30% yield). IR (film): 1790, 1387, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.33 (s, 3H), 1.50 (s, 3H), 2.66−2.74 (m, 2H), 4.81 (d, J = 3.6 Hz, 1H), 4.83 (d, J = 4.0 Hz, 1H), 4.95−5.02 (m, 1H), 5.96 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 174.29, 112.67, 106.19, 85.48, 82.43, 78.03, 35.85, 26.93, 26.47.

5-Deoxy-α-D-glucofuranurono-6,3-lactone (27). A suspension of **25** (194 mg, 0.97 mmol) and Dowex-50w (1.85 g) in water (15 mL) was heated in an oil bath at 70 °C overnight. After vacuum filtration, the filtrate was concentrated to give **27**[40] (0.155 g, 100%) as an off-white solid. IR (KBr): 3380, 1750 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6, ppm): δ 2.50 (d, J = 18.4 Hz, 1H), 2.84 (dd, J = 18.4, 8.4 Hz, 1H), 3.20−3.90 (br, 2H), 4.21 (s, 1H), 4.81 (d, J = 5.6 Hz, 1H), 5.01−5.06 (m, 1H), 5.31 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6, ppm): δ 175.16, 103.45, 87.02, 78.21, 77.70, 37.23.

3,5,6-Tri-*O*-acetyl-2,7,8,9-tetradeoxy-7-phenyl-D-*ido*-nonane-7,8-dienoic Acid, 1,4-Lactone (29). A suspension of **27** (98.9 mg, 0.62 mmol), 3-bromo-1-propynylbenzene (647.7 mg, 3.32 mmol), and indium (286 mg, 2.49 mmol) in 0.1 N hydrochloric acid/ethanol (1:9; 4 mL) was stoppered and stirred vigorously at room temperature overnight. The mixture was vacuum filtered and concentrated to provide a crude product, which was then mixed with 4-(dimethylamino)pyridine (9.2 mg), anhydrous pyridine (8 mL, 104 mmol), and acetic anhydride (5 mL, 49 mmol). After being stirring at room temperature under nitrogen overnight, the solvent was removed under vacuum. Filtration of the reaction mixture through silica gel produced a crude oil, which was subsequently purified by flash chromatography (eluent: 35% ethyl acetate in hexane) to give **29** (121.6 mg, 49%). IR (film): 1940, 1790, 1750, 1200 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 2.01 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.61 (dd, J = 18.4, 6.0 Hz, 1H), 2.86 (dd, J = 18.0, 7.8 Hz, 1H), 4.85 (dd, J = 6.4, 4.0 Hz, 1H), 5.20−5.33 (m, 2H), 5.42 (dt, J = 8.0, 6.0 Hz, 1H), 5.51 (dd, J = 7.2, 4.0 Hz, 1H), 5.95 (d, J = 7.2 Hz, 1H), 7.23−7.28 (m, 1H), 7.32−7.37 (m, 2H), 7.43−7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 20.5, 20.9, 30.30, 34.8, 69.1, 69.9, 70.4, 78.5, 80.9, 103.4, 126.8, 127.8, 128.8, 133.1, 169.1, 169.7, 170.2, 172.4, 209.3. HRMS Calcd for $C_{21}H_{23}O_8$ (M + H): 403.1393; found, 403.1394.

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-β−L-*ido*-furanurono-6,3-lactone (23a). A solution of **31** (4.38 g, 12.6 mmol) and lithium bromide (4.96 g, 57 mmol) in acetone (110 mL) was stoppered and stirred at room temperature for 1 h. After the solvent was removed, the residue was suspended in ether (100 mL) and washed with water (3 × 100 mL) and brine. After being dried over magnesium sulfate and filtered, the solution was concentrated to produce **23a**[23] (3.40 g, 97% yield) as a white solid. IR (film): 1792, 1377, 1169, 1061, 1018 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.34 (s, 3H), 1.52 (s, 3H), 4.25 (s, 1H), 4.84 (d, J = 3.5 Hz, 1H), 4.93 (d, J = 2.9 Hz, 1H), 5.07 (d, J = 2.8 Hz, 1H), 5.97 (d, J = 3.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 170.55, 113.60, 106.87, 84.04, 83.57, 81.32, 38.03, 27.01, 26.48.

5-Bromo-5-deoxy-β-L-*ido*-furanurono-6,3-lactone (32). A solution of **23a** (2.51 g, 9 mmol) in trifluoroacetic acid/water (3:1; 25 mL) was stirred at room temperature for 4.5 h. Removal of solvent under vacuum provided **32** (2.138 g, 98% yield). IR (film): 3400, 1750 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6, ppm): δ 4.28 (s, 1H), 4.46 (s, 1H), 5.05 (d, J = 5.3 Hz, 1H), 5.08 (d, J = 5.0 Hz, 1H), 5.40 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 171.53, 103.74, 85.39, 84.84, 77.17, 41.40. Mp: >125 °C dec. Anal. Calcd for $C_6H_7BrO_5$: C, 30.15; H, 2.95. Found: C, 30.54; H, 2.94.

2-Bromo-7-phenyl-2,7,8,9-tetradeoxy-D-*glycero*-L-*ido*-nonane-7,8-dienoic Acid, 1,4-Lactone (33). A suspension of **32** (102 mg, 0.39 mmol), 3-bromo-1-propynylbenzene (312 mg, 1.6 mmol), and indium (92 mg, 0.8 mmol) in a mixed-solvent system of 0.1 N hydrochloric acid/ethanol (1:9; 6 mL) was stoppered and stirred vigorously at room temperature overnight. After being diluted with ether, the reaction mixture was filtered through Celite and concentrated to give a crude oil (401 mg). Part of the crude oil (60 mg) was purified by preparatory thin-layer chromatography to collect **33** (6 mg, 32% yield). IR (film): 3430, 1938, 1779, 1743 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6, ppm): δ 4.27 (br, 1H), 4.40 (d, J = 7.0 Hz, 1H), 4.56 (d, J = 4.4 Hz, 1H), 4.67 (d, J = 3.8 Hz, 1H), 4.80 (d, J = 3.2 Hz, 1H), 5.26 (s, 2H), 5.67 (br, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.31 (t, J = 7.7 Hz, 2H), 7.51 (d, J = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d_6, ppm): δ 44.7, 69.2, 70.4, 75.2, 80.0, 81.9, 106.7, 126.8, 127.0, 128.4, 134.7, 171.1, 208.7. HRMS Calcd for $C_{15}H_{14}O_4Br$ (M + H − H_2O), 337.0075; found, 337.0075.

2-Bromo-2-deoxy-7-phenyl-D-*erythro*-L-*ido*-heptanoic Acid, 1,4-Lactone (34). A solution of **33** (160 mg) in

(40) Paulsen, H.; Stoye, D. *Chem. Ber.* **1966**, *99*, 908.

methanol (15 mL) cooled to −78 °C was bubbled with ozone until the solution turned blue. After the ozone was flushed out with oxygen, dimethyl sulfide (0.4 mL) was added. The reaction mixture was warmed to room temperature gradually and stirred overnight. Removal of solvent under vacuum provided the crude product (160 mg).

To a solution of the crude product (160 mg) in methanol (15 mL) cooled to −10 °C was added sodium borohydride (45 mg) in one portion. After being stirred for 30 min, the reaction mixture was then quenched with acetic acid (0.6 mL). Removal of solvent under vacuum provided a residue. Without isolation of the product, the residue was stirred with acetic anhydride (15 mL) and concentrated sulfuric acid (0.6 mL) for 5 h before neutralization with a saturated sodium bicarbonate solution (20 mL). The reaction mixture was then extracted with ether (100 mL). The ethereal solution was washed with brine, dried over sodium sulfate, filtered, and concentrated to give **34** (232 mg, 100% yield), in which the two diastereomers were in a ratio of 3:1. An attempt to purify the crude product by flash chromatography led to partial decomposition of the compound. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.87 (s, 3H), 2.06 (s, 3H), 2.14 (s, 3H), 2.15 (s, 3H), 4.25 (d, J = 2.0 Hz, 1H), 4.84 (dd, J = 7.6, 4.4 Hz, 1H), 5.30 (dd, J = 8.8, 1.2 Hz, 1H), 5.43 (dd, J = 4.0, 2.0 Hz, 1H), 5.65 (d, J = 8.8 Hz, 1H), 5.77 (dd, J = 7.6, 1.6 Hz, 1H), 7.26−7.38 (m, 5H). The compound was used directly in the next reaction.

(+)-Goniofufurone (1). To a solution of **34** (49 mg, 70% pure) in methanol/water (9:1; 2 mL), was added sodium bisulfite (7.1 mg) and bisodium sulfite (17.4 mg). The suspension was stirred for 3 h before quenching with 1 N hydrochloric acid (1 mL). The mixture was then extracted with methylene chloride (10 mL). The organic solution was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to provide a crude product (39 mg, 70% pure). A solution of the crude product (39 mg, 70% pure) in methanolic hydrogen chloride (1.5 M, 10 mL) was stirred for 2 days followed by neutralization with sodium bicarbonate powder. The mixture was then diluted with ether and filtered. After removal of solvent, the residue was suspended in ethyl acetate and filtered again. Concentration of the filtrate gave the crude product, which was then purified by preparatory thin-layer chromatography to afford **1**[11] (8.0 mg, 44% yield). Mp: 150−152 °C (lit.:[11] 152−154 °C). IR (film): 3424, 1786, 1047 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O, ppm): δ 2.68 (d, J = 18.8 Hz, 1H), 2.76 (dd, J = 5.6, 18.8 Hz, 1H), 4.09 (dd, J = 2.6, 4.7 Hz, 1H), 4.38 (d, J = 2.6 Hz, 1H), 4.87 (d, J = 4.1 Hz, 1H), 5.11 (dd, J = 4.4, 5.0 Hz, 1H), 5.20 (d, J = 4.7 Hz, 1H), 7.34−7.45 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$ + D_2O, ppm): δ 36.1, 73.5, 74.4, 82.9, 87.4, 125.8, 128.5, 128.8, 138.7, 175.3.

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Supporting Information Available: Experimental procedures for the preparation of compounds **21**−**23**, **26**, and **31**; copies of ^{13}C NMR spectra of **15e**, **19a**, **20a**, **29**, and **33** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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