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Desymmetrization of 1,4-Dien-3-ols and Related Compounds via Ueno−Stork Radical Cyclizations

Félix Villar, Olivier Equey, and Philippe Renaud*

Université de Fribourg, Institut de Chimie Organique, Pérolles, CH-1700 Fribourg, Switzerland

philippe.renaud@unifr.ch

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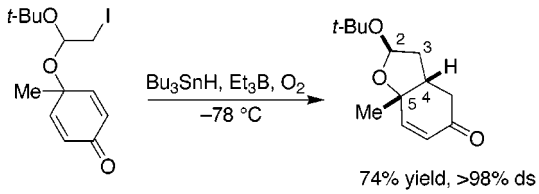
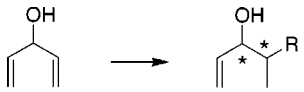
ABSTRACT



Desymmetrization of 1,4-dien-3-ols and related compounds via Ueno−Stork radical cyclizations is reported. The stereochemistry of the cyclization is controlled by the acetal center. Excellent stereocontrol at C(4) and C(5) of the newly formed tetrahydrofuran rings is observed. Use of a chiral auxiliary allows the preparation of enantiomerically pure material. The utility of this method has been demonstrated by achieving a short synthesis of (+)-eldanolide, the pheromone of the male African sugarcane stem borer *Eldana saccharina*.

Desymmetrization of 1,4-dien-3-ols such as 1,4-pentadien-3-ol has been achieved in the past on the basis of epoxidation and hydrosilylation reactions.[1,2] This has led to efficient preparation of useful chiral building blocks. Desymmetrization reactions via formation of carbon−carbon bonds are less developed. In this paper, we have investigated a novel desymmetrization strategy on the basis of a regioselective and diastereoselective formation of a carbon−carbon bond according to Scheme 1. Our approach is taking advantage of a group selective radical addition according to a concept recently reported by Curran.[3]

Scheme 1



The control of the selectivity of the process is achieved by attaching the radical precursor to the alcohol moiety via a haloacetalization process and by running a radical cyclization (Ueno−Stork reaction).[4] Recently, we have demon-

(1) For general reviews on desymmetrization reactions, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213.

(2) For desymmetrization of 1,4-dien-3-ols and related compounds via Sharpless epoxidation, see: Smith, D. B.; Wan, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793−4808. Jäger, V.; Schröter, D.; Koppenhoefer, B. *Tetrahedron* **1991**, *47*, 2195−2210. Hatekeyama, S.; Sakurai, K.; Numata H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201−5203. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber; S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601. Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590−5592. Burke, S. D.; Buchanan, J. L.; Rovin, D. L. *Tetrahedron Lett.* **1991**, *32*, 3961−3964. Belley, M. L.; Hill, B.; Mitenko, M.; Scheigetz, J.; Zamboni, R. *Synlett* **1996**, 92−94. Via hydrosilylation: Tamao, K.; Tohma, T.; Inui, N.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333−7336.

(3) Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron*: *Asymmetry* **1994**, *5*, 199−202. Curran, D. P.; Qi, H.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 8430−8431. Curran, D. P.; Lin, C.-H.; DeMello, N. C.; Junggebauer, J. *J. Am. Chem. Soc.* **1994**, *116*, 8430−8431.

(4) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564−5566. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351−1356. Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741−3742. Stork, G.; Sher, P. M.; Chen H−L. *J. Am. Chem. Soc.* **1986**, *108*, 6384−6385. Stork, G. *Bull. Chem Soc. Jpn.* **1988**, *61*, 149−154. Stork, G. *Bull. Soc. Chim. Fr.* **1990**, *127*, 675−680.

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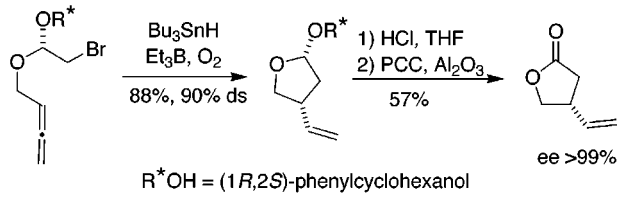
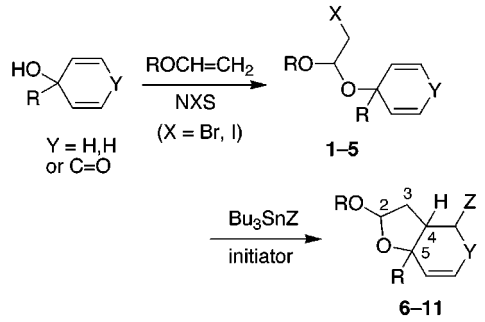
strated that the stereochemical outcome of this reaction could be efficiently controlled from the temporary acetal center as illustrated with the synthesis of 3-vinyl-γ-butyrolactone (Scheme 2)[5] and (±)-botryodiplodin.[6]

Scheme 2



Radical precursors were easily prepared from 1,4-pentadien-1-ol (**1**−**4**) and 1-methyl-2,5-cyclohexadien-4-one (**5**) by haloacetalization with the suitable enol ethers. These compounds were submitted to radical cyclization conditions according to four different procedures (Scheme 3, methods

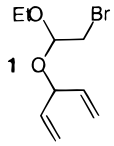
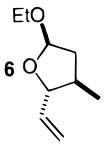
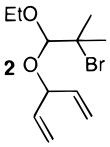
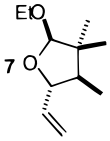
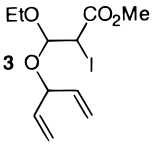
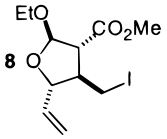
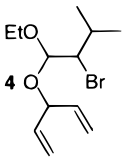
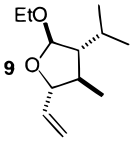
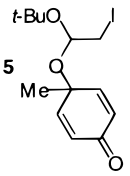
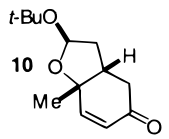
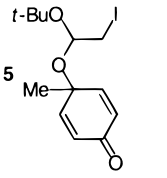
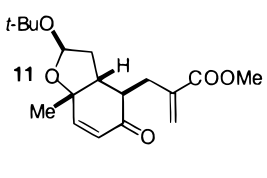
Scheme 3[a]



[a] Method A: Bu_3SnH (Et_3B, O_2), −78 °C. Method B: Bu_3SnH (AIBN), 80 °C. Method C: $(Bu_3Sn)_2$ (AIBN), 10 °C. Method D: $Bu_3SnCH_2C(COOMe)=CH_2$ (AIBN), 80 °C.

A−D).[7] Results are summarized in Table 1. Cyclization of **1** afforded the trisubstituted tetrahydrofuran **6** with total diastereocontrol at −78 °C (entry 1). An important temperature effect was observed in these systems. Running the same reaction at 80 °C afforded the tetrahydrofuran in 86% ds[8] (entry 2). When a *gem*-dimethyl group is introduced at position 3 (numbering according to the tetrahydrofuran moiety, see Scheme 3), a slightly lower diastereoselectivity was observed (entries 3 and 4, 86% ds at −78 °C). When a single substituent is present at position 3, the control of the stereochemistry at the C3 center is rather low (entries 5 and 6) as predicted by the Beckwith−Houk radical cyclization model[9]. Indeed, the alkoxy group at position 2 favors the trans relative configuration and the substituent at position 4 favors the cis configuration. This effect has already been noticed in simple Ueno−Stork radical cyclizations controlled by the

Table 1. Radical Cyclizations According to Scheme 3

entry	precursor	product[a,b]		
				
1	Meth. A (–78 °C)		65% y	>98% ds
2	Meth. B (80 °C)		61% y	86% ds
				
3	Meth. A (–78 °C)		75% y	>86% ds
4	Meth. B (80 °C)		88% y	74% ds
				
5	Meth. C (10 °C)		71% y	77% ds[c]
				
6	Meth. A (–78 °C)		66% y	63% ds[c]
				
7	Meth. A (–78 °C)		74% y	>98% ds
8	Meth. B (80 °C)		71% y	89% ds
				
9	Meth. D (80 °C)		68% y	81% ds

[a] Only the major isomer is drawn. [b] The diastereoselectivity is expressed as % ds, see ref 8 for the definition. [c] The principal minor isomer is the epimer at C(3).

acetal center.[6] However, two out of the three newly formed centers (C4 and C5) are created with high stereocontrol. The cyclic radical precursor **5** gave also excellent level of stereocontrol at low temperature (entry 7 and 8, >98% ds at −78 °C). Interestingly, the reaction with (2-methoxycar-

(5) Villar, F.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 8655−8658.
(6) Villar, F.; Andrey, O.; Renaud, P. *Tetrahedron Lett.* **1999**, *40*, 3375−3378.

bonylpropenyl)tributylstannane afforded the α-alkylated bicyclic ketone **11** with satisfactory diastereoselectivity (entry 9).

The stereochemical outcome of these reaction is rationalized by transition states of type **A** (chairlike) and **B** (boatlike) for the open and the cyclic systems, respectively (Figure 1).

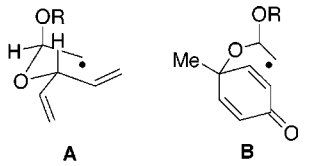
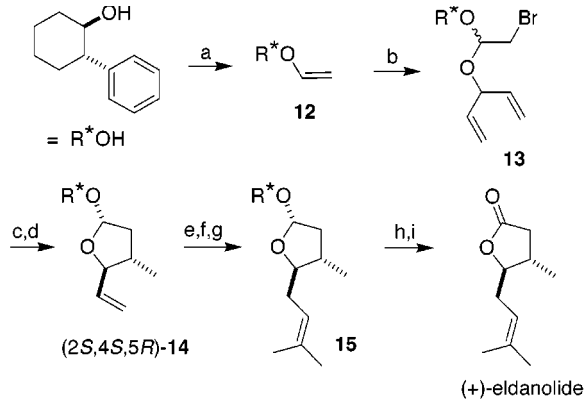


Figure 1. Model for the stereochemical outcome of radical cyclizations starting from **1** (A) and **5** (B).

In these models, the systems adopt a conformation where the anomeric effect at the acetal center is maximized.[9,10] These simple models are supported by ab inito calculations that will be reported in a forthcoming full paper.

The utility of this approach was demonstrated by the preparation of the naturally occurring (+)-eldanolide, the pheromone of the male African sugarcane stem borer *Eldana saccharina* (Scheme 4).[11] For this purpose, the bromoacetal

Scheme 4. Synthesis of (+)-Eldanolide[a]



[a] Key: (a) ethyl vinyl ether, $Hg(OAc)_2$, 70%; (b) 1,4-pentadien-3-ol, NBS, 75% (1:1 mixture of diastereomer); (c) Bu_3SnH, Et_3B, O_2, 85%, ds >98%; (d) chromatography; (e) 9-BBN then H_2O_2, NaOH, 93%; (f) CO_2Cl_2, DMSO, 95%; (g) $Ph_3PC(CH_3)_2$, 51%; (h) HCl, H_2O, 68% [(1*R*,2*S*)-2-phenylcyclohexanol recovered in 62%]; (i) PCC, Al_2O_3, 73%.

13 was prepared from (1*R*,2*S*)-2-phenylcyclohexanol via mercury(II)-catalyzed transetherification and bromoacetalization with 1,4-pentadien-3-ol. The haloacetalization step is not stereoselective, the required diastereomerically pure **13** could be obtained after flash chromatography; however, since the separation of the diastereomers is easier after the cyclization reaction, the mixture of diastereomers was used for the next step. A study of the stereochemistry of the haloacetalization step is currently underway. Interestingly, good stereocontrol are now routinely achieved with vinyl ether derived from *O*-monomethylbinaphthol and (1*R*)-3-[*N*-(3,5-dimethylphenyl)benzenesulfanamido]isoborneol.[12] The bromoacetal **13** (1:1 mixture of two diastereomers) was submitted to cyclization conditions to afford **14** as a 1:1 mixture of two diastereoisomers; the cyclization process is completely diastereoselective (ds > 98%) for each diastereomer of **13**. At this stage, the two diastereomers were separated by flash chromatography, and (2*S*,4*S*,5*R*)-**14** was used for the rest of the synthesis. The γ-chain was modified in a straightforward manner by hydroboration, Swern oxidation, and Wittig reaction. Finally, hydrolysis of the acetal **15** furnished the lactol together with recovered (1*R*,2*S*)-2-phenylcyclohexanol (62%). Oxidation of the lactol with PCC gave enantiomerically pure (+)-eldanolide (optical purity checked by gas chromatography on a chiral column, see Supporting Information).

Finally, we have investigated a similar desymmetrization process for 1,6-heptadien-4-ol. The bromoacetal **16**, when treated with Bu_3SnH in the presence of triethylborane and oxygen at −78 °C, gave **17**, the product of a 6-*exo*-*trig* cyclization, in 43% yield with complete stereocontrol (Scheme 5). The moderate yield is due to the formation of acyclic reduced product. The relative configuration was deduced from the ^1H NMR coupling constant, and the methyl

(7) Procedure A: A solution of the haloacetal (2.1 mmol) and Bu_3SnH (735 mg, 2.5 mmol) in toluene (52 mL) was cooled at −78 °C, and a 1 M solution of Et_3B in hexane (2.9 mL, 2.9 mmol) was added followed by air (2.0 mL). The solution was kept at −78 °C for 3 h. A 1 M NaOH solution (30 mL) was added, and the heterogeneous mixture was stirred for 2 h at room temperature. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane/Et_2O). Procedure B: A solution of Bu_3SnH (735 mg, 2.52 mmol), AIBN (17 mg), and the haloacetal (2.1 mmol) in benzene (20 mL) was heated under reflux. The reaction was followed by TLC until all starting material disappeared. Workup as in procedure A. Procedure C: A solution of the haloacetal (1 mmol) and $(Bu_3Sn)_2$ (58 mg, 0.1 mmol) in benzene (5 mL) was irradiated with a sun lamp at 10 °C until all starting material disappeared (approximately 2 h). A KF aqueous solution was added, and the mixture was stirred for 2 h. The organic layer was washed with H_2O, dried, and evaporated. The crude product was purified by flash chromatography (hexane/Et_2O). Procedure D: A solution of (2-methoxycarbonylpropenyl)tributylstannane (1.55 g, 4 mmol), AIBN (4 mg), and the haloacetal (0.5 mmol) in benzene (5.5 mL) was heated under reflux. The reaction was monitored by TLC until all starting material disappeared. Workup as in procedure A.

(8) The diastereoselectivity is expressed as % ds, the percentage of a certain diastereomer in a mixture of two or more diastereomers: Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer: Berlin, 1986; pp 125−259.

(9) For the Beckwith−Houk transition state model, see: (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974. For a discussion of the stereochemistry in Ueno−Stork cyclization reactions controlled by the acetal center, see refs 5 and 6 and: Beckwith, A. L. J.; Page, D. M. *J. Org. Chem.* **1998**, *63*, 5144−5153.

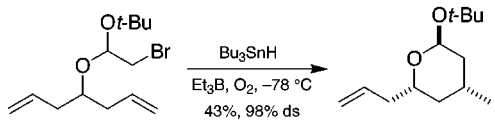
(10) The importance of the anomeric effect in Ueno−Stork radical cyclization has already been studied by Fraser-Reid in carbohydrate derivatives: Lopez, J.-C.; Gomez, A. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1533−1534. Lopez, J.-C.; Gomez, A. M.; Fraser-Reid, B. *Aust. J. Chem.* **1995**, *48*, 333−352. Lopez, J.-C.; Fraser-Reid, B. *Chem. Commun.* **1997**, 2251−2257.

(11) Isolation: Vigneron, J.-P.; Méric, R.; Larchevêque, M.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521−3529. Synthesis using a Ueno−Stork radical cyclization: Itoh, T.; Sakabe, K.; Kudo, K.; Zagatti, P.; Renou, M. *Tetrahedron Lett.* **1998**, *39*, 4071−4074.

(12) Villar, F.; Renaud, P. Manuscript in preparation.

(13) Recently, Beckwith has observed a similar trans relationship in a related 6-exo-cyclization reaction; see ref 10.

Scheme 5



16 **17**

at position 4 is trans relative to the *tert*-butoxy group and cis to the allyl group.[13]

In conclusion, we have demonstrated in this paper that desymmetrization of 1,4-dien-3-ols and related compounds via Ueno−Stork radical cyclization proceeds very efficiently. Utilization of this approach for the synthesis of enantiomerically pure natural products has been demonstrated. A crucial point for this strategy, i.e., the control of the relative configuration at the acetal center during the bromoacetalization of chiral enol ethers, is under investigation and will be reported in due course.

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Supporting Information Available: Experimental details for all procedures including full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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