Functionalization via Radical Cyclization of Cyclohexenediol Derivatives Bound to Polystyrene

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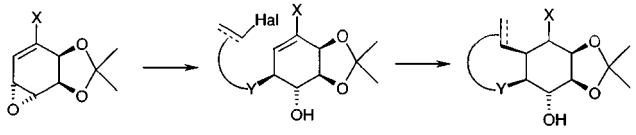
Received 26 April 1999

Abstract: Radical cyclization reactions involving precursors derived from cyclohexadiene diols were investigated, both, in solution and on the solid phase. A straightforward sequence was established in solution to obtain bicyclic compounds with potential for diversity. Optimized reaction procedures were applied to solid phase synthesis.

Key words: Solid phase synthesis, epoxide opening, radical cyclization

The emergence of combinatorial chemistry stimulated intensive efforts in the application of reactions broadly used in solution to the solid phase synthesis.[1] While a number of reaction conditions have been widely applied to the solid support, examples for radical reactions on solid phase are still limited to only a few.[2] Recently, we demonstrated that (1S,2S)-3-halocyclohexa-3,5-diene-1,2-diols, which are readily available through fermentation of the corresponding halobenzenes, can be used as valuable and versatile building blocks in solid phase chemistry.[3] In this paper we describe radical cyclization reactions with this substrate.

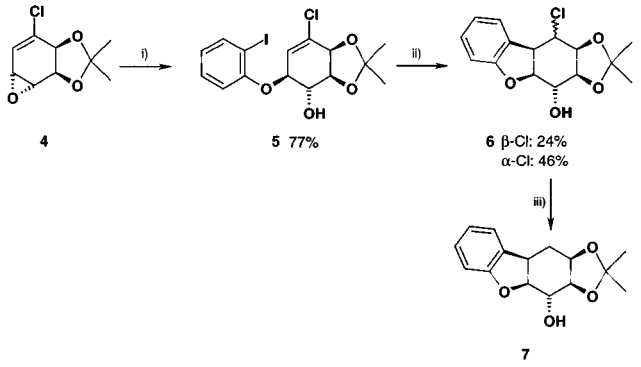
The general strategy of this approach is outlined in Scheme 1. Epoxide opening of **1** with a nucleophile carrying vinylic or arylic iodide or bromide should give structures of type **2**, which should be prone to radical cyclization upon homolytic cleavage of the halogen-carbon bond to give *cis* fused bicyclic compounds **3**.



Scheme 1. General strategy for radical cyclization starting form **1**.

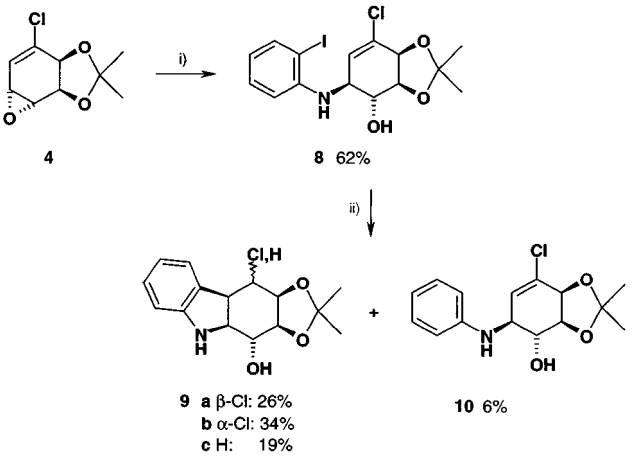
This hypothesis was first tested with compound **5**, obtained in 77% yield from epoxide **4**,[4] which cyclized readily when treated with one equivalent of nBu$_3$SnH and AIBN in refluxing benzene to give **6** as a mixture of diasteromers (Scheme 2) in 70% yield. Treatment of **6** with excess of nBu$_3$SnH resulted in reduction of the chloride to **7**.

In analogy, compound **8**, derived from Lewis acid assisted epoxide opening of **4** with 2-iodoaniline (clean epoxide



Scheme 2. i) 2 eq. 2-iodophenol, 1.1 eq. Schwesinger base,[6] dioxane, 0°C then 100°C 24h; ii) 1.1 eq. nBu$_3$SnH, 0.1 eq. AIBN, benzene (0.05M), reflux 7h; iii) 2 eq. nBu$_3$SnH, 0.1 eq. AIBN, benzene (0.05M), reflux, 17h.

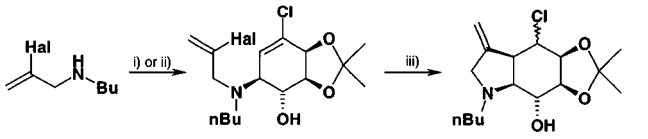
openings with anilines were only accomplished through this lewis acid catalysis),[5] gave a mixture of the chloride containing epimers **9a**,**b** as well as the over reduced compound **9c** and some non-cyclized, reduced compound **10** (Scheme 3). Only the β- derivative **9a** and **10** could be isolated in pure



Scheme 3. i) 2 eq. 2-iodoaniline, 50 mM LiBPh$_4$, 2,6-lutidine, 15h RT, 2h, 50°C; ii) 1.4 eq. nBu$_3$SnH, 0.15 eq. AIBN, benzene (0.01M), reflux, 24h.

form, **9b** and **9c** were inseparable by flash chromatography and isolated together in 53% combined yield in a ratio of 1.79:1 (determined by ^{1}H-NMR). Epoxide **4** was also reacted with vinylhalides **11** and **12** in 50 mM LiClO$_4$/2,6-lutidine to give compounds **13** and **14** in excellent yields

(Scheme 4). When treated with a slight excess of nBu$_3$SnH and catalytic AIBN both, the vinyl iodide and the vinyl bromide, cyclized readily to compound **15** as a mixture of diastereomers. Acetylene **16** reacted through radical addition of nBu$_3$SnH followed by cyclization to give a mixture of vinylstannanes **17a**,**b**,**c** in 48% yield (Scheme 5). In the crude product, **17a**,**b**,**c** were present in a ratio of 72:8:20. Upon flash chromatography, only β-isomer **17a** could be isolated in pure form, while **17b**,**c** were obtained as a mixture in combined 15% yield.

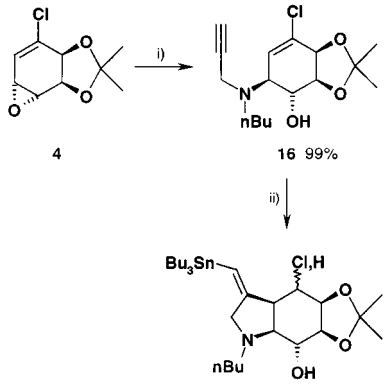


11 Hal = I
12 Hal = Br

13 Hal = I, 92%
14 Hal = Br, 99%

15 crude: β:α = 65:35
isolated: 49% β, 25% α

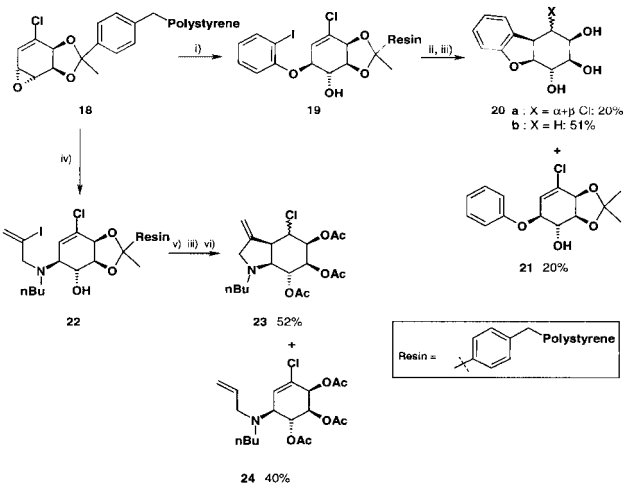
Scheme 4. i) 2 eq. butyl-(2-iodo-allyl)-amine, 50 mM $LiClO_4$, 2,6-lutidine, 50°C, 50h; ii) 2 eq. butyl-(2-bromo-allyl)-amine, 50 mM $LiClO_4$, 2,6-lutidine, 50°C, 4.5h; iii) 1.1 eq. nBu$_3$SnH, 0.05 eq. AIBN, benzene (0.01M), reflux, 2.5h.



17 **a** β-Cl: 72% crude, 33% isolated
b α-Cl: 8% crude, 5% isolated together with **17c**
c H: 20% crude, 10% isolated together with **17b**

Scheme 5. i) 2 eq. butyl-prop-2-ynyl-amine, 50 mM $LiClO_4$, 2,6-lutidine, 50°C, 3h; ii) 1.7 eq. nBu$_3$SnH, 0.25 eq. AIBN, benzene (0.01M), reflux, 24h.

The above examples demonstrated the synthesis of highly functionalized bicyclic systems from readily available starting materials through radical cyclizations in solution. Therefore, we repeated this strategy on a solid phase bound substrate. As indicated in Scheme 6, the reaction proceeded well on resin bound substrates, even though larger amounts of reduced, non-cyclized products were obtained. Solid phase bound epoxide **18**[3a] reacted with 2-iodophenol in the presence of Schwesinger base at 100 °C.[6] The resulting intermediate **19** was treated in nine portions with AIBN and nBu$_3$SnH. Upon acidic cleavage from the resin a mixture of **20a**,**b** (71%) was obtained together with non cyclized compound **21** (20%). The cyclization of **22**, which was synthesized from **18**, gave similar results: upon acylation of the crude reaction products compounds **23a**,**b** as well as substantial amounts of reduced compound **24** were isolated.

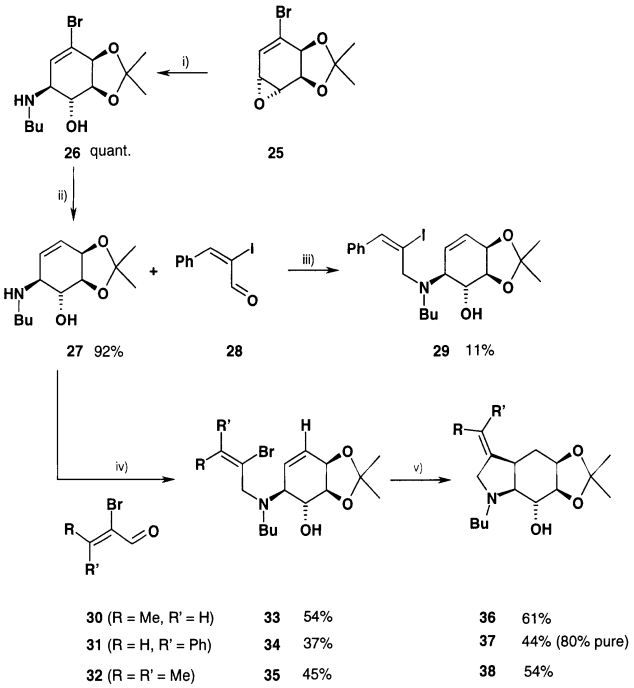


Scheme 6. i) 6 eq. 2-iodophenol, 6 eq. Schwesinger base,[6] dioxane, 100°C, 90h; ii) 14.5 eq. (9×0.5+1×10) nBu$_3$SnH, 1.9 eq. (9×0.1+2×0.5) AIBN, benzene (0.05M), reflux, 80h; iii) $CF_3CO_2H/H_2O/CH_2Cl_2$ (5/1/94), RT, 1h; iv) 5 eq. butyl-(2-iodo-allyl)-amine, 50mM $LiClO_4$, 2,6-lutidine, 50°C, 21h; v) 3 eq. (6×0.5) nBu$_3$SnH, 0.6 eq. (6×0.1) AIBN, benzene (0.05M), reflux, 48h; vi) 20 eq. Ac_2O, 10 eq. Et_3N, pyridine, RT, 16h.

We were not able to achieve complete reduction of compounds **20a** through additional nBu$_3$SnH/AIBN during the cyclization reaction without increasing the yield of undesired **21**. We, therefore, decided to improve our synthetic strategy by removing the vinylic halogen present in the starting material. Product mixtures derived from incomplete reduction during the cyclization step could then be avoided.

We addressed this problem by removing the vinylic halogen present in the starting material. At the same time we made the sequence more convergent, which would allow us to readily introduce diversity. This sequence was first established in solution. Treatment of **26** with tBuLi followed by an acidic quench gave compound **27** (Scheme 7).[7] A number of different conditions were examined to effect reductive alkylation with vinyl iodide **28**. However, only the use of $NaBH(OAc)_3$ in CH_2Cl_2 allowed for isolation of 11% product. We reasoned that less hindered bromides would react much more readily in the amine alkylation sequence. Indeed, when unsaturated aldehydes **30**-**32**[8] were reacted with **27**, better yields of the corresponding alkylated products were obtained (37%-54%). The resulting product **33**-**35** were cyclized with nBu$_3$SnH/AIBN to give the corresponding bicyclic systems. Due to the rather modest yield of this sequence (Scheme 7) we did not undertake the preparation of a library of compounds. In conclusion, we have demonstrated that cyclohexadienes can be efficiently derivatized to highly functionalized polycycles in a reaction sequence involv-

ing epoxidation, epoxide opening with suitable nucleophiles, followed by radical cyclizations. Several examples demonstrated the feasibility of this approach for solid phase chemistry.[9]



Scheme 7. i) 2 eq. $BuNH_2$, dioxane, 80°C, 12h; ii) 3.2 eq. ^tBuLi, THF, -78°C, 1h, then H_2O; iii) 1.3 eq. aldehyde, 1.4 eq. $NaBH(OAc)_3$, CH_2Cl_2, RT, 8h; iv) 1.3 eq. aldehyde, 1.3-2.4 eq. $NaBH(OAc)_3$, CH_2Cl_2, RT, 15-24h; v) 1.1-3.3 eq. n-Bu_3SnH, 0.05-0.15 eq. AIBN, benzene, reflux, 1.5-48h.

References and Notes

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(9) Representative protocols for reactions on the solid phase: **18**→**19**:2-Iodophenol (428 mg, 1.94 mmol) was dissolved in dioxane (5 ml) and cooled to 0 °C. 2-*Tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorin (521 µl, 1.94 mmol) was added. The resulting phenolate was added to as suspension of **18** (600 mg, 0.324 mmol) in dioxane (10 ml) and the mixture was heated to reflux for 90 h. The reaction was cooled to room temperature, the solid phase was filtered and washed with 5 ml each of dioxane (6 x), H_2O (6 x), H_2O:EtOH (1:1, 6 x), EtOH (6 x) dioxane (6 x), MeOH, CH_2Cl_2 (alternating, 6 x), and Et_2O (3 x). In order to determine the yield and purity of the product, a fraction (67 mg) of the resin was treated with CF_3COOH : H_2O : CH_2Cl_2 (5:1:94) for 1.5 h, filtered, and the resin was washed with THF and MeOH. The combined organic phases were concentrated and twice coevaporated with toluene. The crude product (quantitative yield) was analyzed by ^{1}H NMR(400 MHz) and shown to be >80% pure.
19→**20**, **21**:**19** (205 mg, 0.1 mmol) was suspended in degassed benzene and heated to reflux under an argon atmosphere. n-Bu_3SnH (200 µl of the 0.25 M solution in degassed benzene, 0.05 mmol) and AIBN (100 µl of the 0.1 M solution in degassed benzene, 0.01 mmol) were added. 8 Additional such additions of n-Bu_3SnH and AIBN were made in 0.5 h intervals. At this point (after 4.5 h) an excess of n-Bu_3SnH (4 ml of a 0.25 M solution in benzene) and AIBN (0.5 ml of a 0.1 M solution in benzene) were added and the reaction mixture was refluxed for 12 h. The mixture was cooled to room temperature, the solid phase was filtered and washed with 4 ml each of dioxane (6 x), toluene (6 x), hexane (6 x), CH_2Cl_2 (6 x), EtOH (6 x), dioxane (6 x), CH_2Cl_2, MeOH (alternating, 3 x), CH_2Cl_2 (1 x) and Et_2O (3 x). The resin was dried under high vacuum (to give 196 mg) and treated with CF_3COOH : H_2O : CH_2Cl_2 (5:1:94, 3.3 ml) for 1.5h at room temperature. The resin was filtered and washed with THF (3 ml) and MeOH (3 ml). The combined organic layers were concentrated and dried under high vacuum to give 19.8 mg of the crude product mixture **20a**,**b**, **21**.[7] Selected 1H NMRdata for **20b**:^{1}H NMR (400 MHz, CD_3OD): δ = 7.06 (d, 1H, arom); 6.94 (d, 1H, arom); 6.72 (t, 1H, arom); 6.63 (d, 1H, arom); 4.39 (dd, 1H, C*H*OH); 3.93 (m07, 1H, C*H*Ar), 3.86 (dd, 1H, C*H*OH); 3.45 (m, 2H, C*H*OH and C*H*OAr); 2,06 (m, 2H, CH_2); 1.88 (m, 2H, CH_2).

Article Identifier:
1437-2096,E;1999,0,07,1121,1123,ftx,en;L02999ST.pdf