Tetrahedron Letters 49 (2008) 6787–6790

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stille reaction over *cis*-halocyclohexadienediol derivatives

Viviana Heguaburu [a,*], Marcus Mandolesi Sá [b], Valeria Schapiro [a], Enrique Pandolfi [a]

[a] Departamento de Química Orgánica, Facultad de Química, UdelaR, Montevideo, C.P. 11800, Uruguay
[b] Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC 88040-900, Brazil

ARTICLE INFO

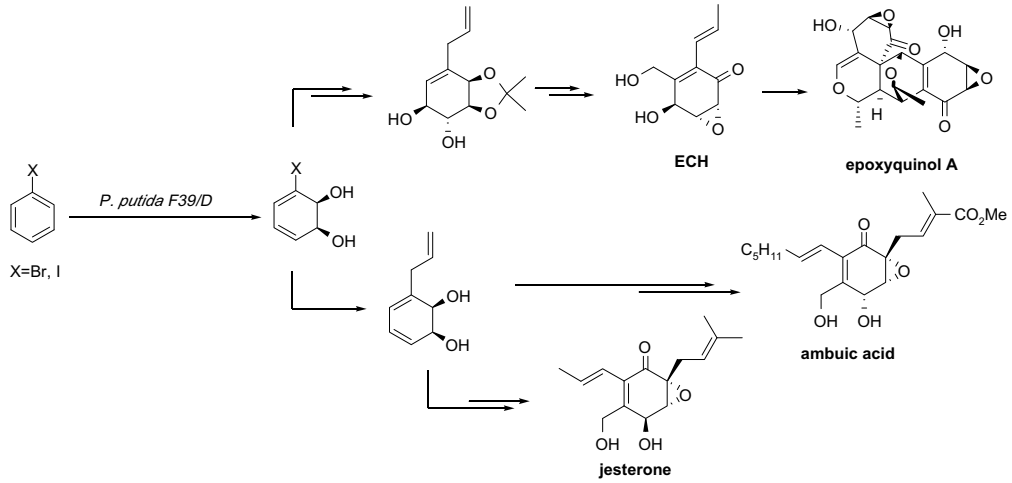
Article history:
Received 17 July 2008
Revised 5 September 2008
Accepted 10 September 2008
Available online 17 September 2008

Keywords:
cis-Cyclohexadienediols
Stille reaction
Microwave

ABSTRACT

Stille reaction was performed with several halo *cis*-diol derivatives by reaction with allyltributyltin in the presence of a palladium catalyst forming allyl *cis*-dihydrodiol derivatives. These couplings were conducted with conventional heating as well as with microwave irradiation. Allylbenzene *cis*-dihydrodiol was obtained with excellent yield using mild conventional heating. However, if the diol moiety is protected with the isopropylidene group, the expected product is obtained only under microwave irradiation. The unusual reactivity observed for the polyoxygenated derivatives suggests assistance of the free hydroxyls in the catalytic cycle.

Biotransformation of monosubstituted arenes by mutant strains of *Pseudomonas putida*[1] to produce *cis*-dihydrodiols is a valuable process[2] leading to homochiral synthons, which are useful in asymmetric synthesis of natural products.[3,4] Although there are more than 400 *cis*-arene diols known, low production yields and substrate specificity of the enzyme involved in this transformation limit the synthetic possibilities of these multifunctional compounds. In order to expand the utility of these *cis*-diols, it is highly desirable to increase the variety of these compounds available, with different motifs in their side chain. Up to now, there have been only a few reports aiming at this goal, such as Boyd's[5,6] palladium-catalyzed cross-coupling of unprotected *cis*-diols, Hudlicky's preparation of alkynes[7] and Ley's preparation of organostannanes as Stille cross-coupling partners.[8] Also, results concerning the side chain modification of *cis*-diols on previously functionalized rings have been reported.[9–15]

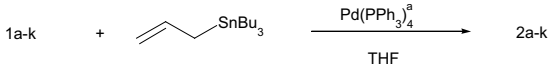


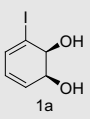
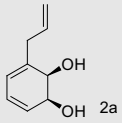
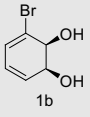
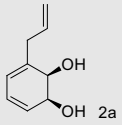
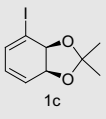
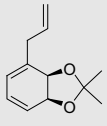
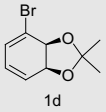
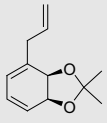
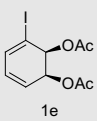
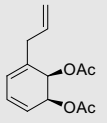
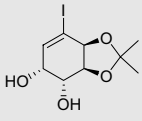
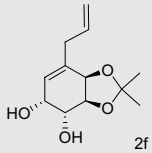
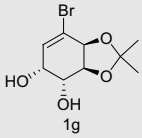
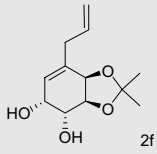
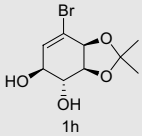
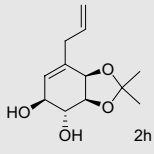
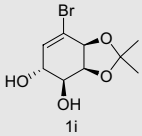
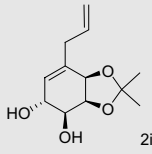
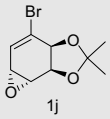
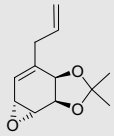
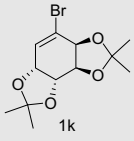
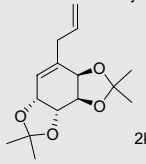
Scheme 1. Synthetic strategy for chiral epoxyenones by side chain modification of *cis*-diols.

* Corresponding author. Tel.: +598 2 9244066; fax: +598 2 9241906.
E-mail address: vheguab@fq.edu.uy (V. Heguaburu).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.049

Table 1
Stille cross-coupling of allyltributyltin and *cis*-cyclohexadienediols and derivatives under conventional heating



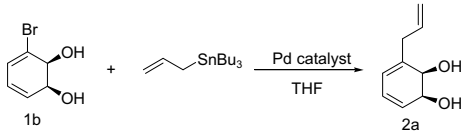
Entry	Reactant (**1a–k**)	Temp (°C)	Time (hs)	Product (**2a–k**)	Yield (%)
1	 1a	35	0.45	 2a	93
2	 1b	Reflux	8	 2a	20
3	 1c	Reflux	8	 2c	No reaction
4	 1d	Reflux	8	 2c	No reaction
5	 1e	35	3	 2e	72
6	 1f	Reflux	3	 2f	90
7	 1g	Reflux	12	 2f	70
8	 1h	Reflux	12	 2h	25
9	 1i	Reflux	12	 2i	49
10	 1j	Reflux	10	 2j	No reaction
11	 1k	Reflux	12	 2k	Traces

[a] All reactions were carried out using 15 mol % of palladium catalyst.

We based our study on Boyd's work[5] in which *cis*-cyclohexadienediols reacted with allyltributyltin in the presence of a palladium catalyst to replace bromine or iodine by an allyl group, forming allyl *cis*-dihydrodiols in low to moderate yields. We studied this reaction over several *cis*-dihydrodiol derivatives in order to obtain valuable synthons for our research program in natural products synthesis.[16] Insertion of allylic side chain into *cis*-diol derivatives combined with modern synthetic methodologies is currently the focus of our research, in order to achieve the total synthesis of chiral epoxyenones, such as epoxyquinols, ambuic acid, jesterone and related compounds (Scheme 1).[17] In this Letter, we present our results involving the Stille cross-coupling of allyltributyltin and several *cis*-diols and derivatives, under conventional heating and microwave irradiation, to obtain proper synthons for our research program.

Stille reactions were conducted with conventional heating (oil bath) as well as with microwave irradiation.[18] Allylbenzene *cis*-dihydrodiol (Table 1, entry 1, **2a**) was obtained with excellent yield by reaction of iodo precursor **1a** with allyltributyltin under mild heating. Despite Boyd's work in which bromo *cis*-cyclohexadienediol **1b** did not react at 35 °C, the product **2a** could be obtained at a higher temperature. However, the reaction yield was lower than the one obtained with the iodo derivative. Compound **2a** showed to be unstable in mild acidic conditions rendering aromatic products. As functionalization grows on the cyclic structure, this type of compounds becomes more stable. Protected *cis*-diols, as well as further functionalized derivatives are also suitable synthons for our synthetic purposes. A very common way to prevent aromatization of *cis*-dihydrodiols is to protect the diol moiety with the isopropylidene group (**1c,d**). The isopropylidene group also blocks one face of the cyclohexadiene, hence directing the stereochemical outcome of the reaction.[3] However, when Stille cross-coupling was performed with substrates containing the isopropylidene group, no reaction was achieved (Table 1, entries 3 and 4). These results suggest that steric hindrance of this protective group does not allow the reaction to occur. When iodo *cis*-dihydrodiol is protected as its diacetate (**1e**), cross-coupling occurs in 3 h at 35 °C in 72% yield (entry 5), supporting the hypothesis that the steric effect plays an important role in this reaction. However, polyoxygenated derivatives **1f–i**[19–21] afforded the expected products even when they are partially protected as acetonides. These results indicate that an assistance of the free allylic hydroxyl in the palladium catalytic cycle may occur.[22,23] In an effort to confirm these hypothesis, compounds **1j** and **1k** were submitted to the same cross-coupling conditions. Reaction of the sterically hindered derivative **1k** only afforded small amounts of **2k**, and compound **1j** showed no reaction. A more detailed observation of the results in

Table 2
Stille reaction of *cis*-diol **1b** under various conditions



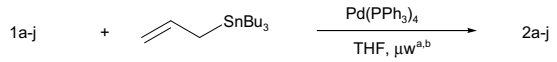
Entry	Source of heating[a]	Pd catalyst (mol %)	Temperature (°C)	Time (min)	Yield
1	Oil bath	$Pd(PPh_3)_4$ (15%)	Reflux	480	20
2	Microwave	$Pd(PPh_3)_4$ (15%)	90	5	15
3	Microwave	$Pd(PPh_3)_4$ (7%)	90	5	7
4	Microwave	$Pd(PPh_3)_4$ (15%)	90	10	38
5	Microwave	$Pd(PPh_3)_4$ (15%)	100	6	42
6	Microwave	$PdCl_2(PPh_3)_2$ (15%)	100	6	12
7	Microwave	$Pd(PPh_3)_4$ (15%)	120	6	13

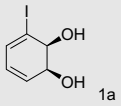
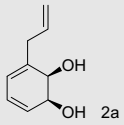
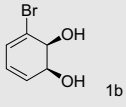
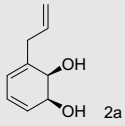
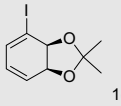
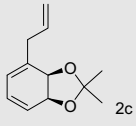
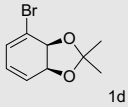
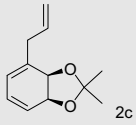
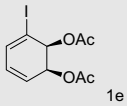
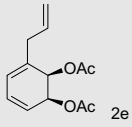
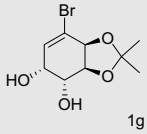
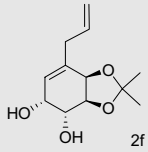
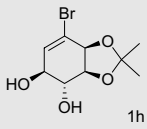
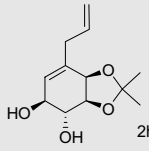
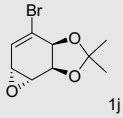
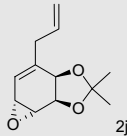
[a] Microwave reactions were carried out using 200 W power.

Table 1 (entries 7–9) shows that compounds **1g** and **1i** were converted to the corresponding allyl derivatives in higher yields than **1h**. These results outline the importance of the presence of an allylic hydroxyl moiety at the coupling partner, specially when it is arranged at the less hindered face, opposite to the isopropylidene group.

Stille reactions were also conducted under microwave conditions to study a possible improvement in the reaction rates and yields. Reaction of **1b** was studied in detail in order to define the best conditions for microwave heating. Time, temperature, catalyst and catalyst load were varied. These results are showed in Table 2.

Table 3
Stille cross-coupling of allyltributyltin and *cis*-cyclohexadienediols and derivatives under microwave irradiation



Entry	Reactant (**1a**–**h**)	Temp (°C)	Time (min)	Product (**2a**–**h**)	Yield (%)
1	 1a	100	6	 2a	67
2	 1b	100	6	 2a	42
3	 1c	120	6	 2c	16
4	 1d	120	6	 2c	38
5	 1e	90	10	 2e	27
6	 1g	100	10	 2f	43
7	 1h	100	10	 2h	21
8	 1j	100	10	 2j	No reaction

[a] All reactions were carried out using 200 W power.
[b] All reactions were carried out using 15 mol % of palladium catalyst.

Lowering the catalyst load affected the reaction course (entry 3). The reaction yield can be improved by using a longer irradiation time (entry 4), as well as raising the temperature to 100 °C (entry 5). However, at 120 °C the reaction yield decreased, probably due to catalyst decomposition and formation of oxidative addition products.[24] When the catalyst was changed to $PdCl_2(PPh_3)_3$, the reaction did not work in a satisfactory manner (entry 6).

Once the reaction conditions for **1b** were optimized, microwave reactions were extended to a variety of derivatives. As shown in Table 3, when the diol moiety was protected with isopropylidene group (**1c and d**, entries 3 and 4) the expected product was obtained in modest yields by microwave irradiation at higher temperatures. In general, higher reaction times did not afford better conversions. These preliminary results indicated that cross-coupling can be significantly accelerated under microwave-assisted conditions, but a finer tuning of the reaction parameters must be performed in order to achieve higher yields.

In conclusion, Stille reaction has been successfully performed with *cis*-dienediols and derivatives.[25,26] These transformations are promoted by oxygenated groups such as free hydroxyls or acetates. Results obtained with polyoxygenated derivatives suggest an assistance of the free allylic hydroxyl in the catalytic cycle. Also, it is demonstrated that higher yields were obtained when the assisting hydroxyl is placed at the less hindered face. However, if the diol is protected with an isopropylidene group, the coordination to the palladium species is more difficult due to steric restrictions and the reaction did not take place under conventional heating. The use of microwave irradiation improves reaction rates and yields in a significant way for isopropylidene-protected *cis*-cyclohexadienediols, in comparison with conventional heating.

Stille cross-coupling proved to be a valuable tool to obtain proper building blocks for the synthesis of chiral epoxyenones. Extension of this coupling protocol for the synthesis of natural products of this type is currently under investigation and will be reported in due course.

Acknowledgements

The authors are grateful to PEDECIBA (PNUD/URU/06/004) and CSIC-UdelaR for financial support of this work. V.H. thanks PEDECIBA and ANII for a doctoral fellowship. Research Grants from CNPq and FAPESC (PRONEX-2003, Brazil) are also acknowledged. We are also grateful to Diego Menesez and Dr. David González for helpful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.049.

References and notes

1. Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653–2662.
2. Hudlicky, T.; Stabile, M.; Gibson, D. T.; Whited, G. M. *Org. Synth.* **1999**, *76*, 77–85.
3. Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35–61.
4. Johnson, R. A. *Org. React.* **2004**, *63*, 117–264.
5. Boyd, D. R.; Hand, M. V.; Sharma, N. D.; Chimia, J.; Dalton, H.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1991**, 1630–1632.
6. Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H. *J. Chem. Soc., Perkin Trans.1* **1998**, 1935–1943.
7. Hudlicky, T.; Boros, E. *Tetrahedron: Asymmetry* **1992**, *3*, 217–220.
8. Ley, S.; Redgrave, A. J.; Taylor, S. T.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741–742.
9. Johnson, C. R.; Johns, B. A. *J. Org. Chem.* **1997**, *62*, 6046–6050.
10. Hudlicky, T.; Tian, X.; Konigsberg, K.; Rouden, J. *J. Org. Chem.* **1994**, *59*, 4037–4039.
11. Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.; Berteina, S. *Acc. Chem. Res.* **2000**, *33*, 215–224.

12. Bellomo, A.; Gonzalez, D.; Stefani, H. A. *J. Organomet. Chem.* **2008**, *693*, 1136–1142.
13. Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T. *Tetrahedron: Asymmetry* **1997**, *8*, 975–977.
14. Matveenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron* **2008**, *64*, 4817–4826.
15. Bui, V. P.; Nguyen, M.; Hansen, J.; Baker, J.; Hudlicky, T. *Can. J. Chem.* **2002**, *80*, 708–713.
16. Schapiro, V.; Cavalli, G.; Seoane, G.; Faccio, R.; Mombrú, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2453–2459.
17. Labora, M.; Heguaburu, V.; Pandolfi, E.; Schapiro, V. *Tetrahedron: Asymmetry* **2008**, *19*, 893–895.
18. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
19. Fonseca, G.; Seoane, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1393–1402.
20. Brovetto, M.; Schapiro, V.; Cavalli, G.; Padilla, P.; Sierra, A.; Seoane, G.; Suescun, L.; Mariezcurrena, R. *New J. Chem.* **1999**, *23*, 549–556.
21. Hudlicky, T.; Restrepo-Sánchez, N.; Kary, P. D.; Jaramillo-Gómez, L. M. *Carbohydr. Res.* **2000**, *324*, 200–203.
22. Dominguez, B.; Pazos, Y.; De Lera, A. *J. Org. Chem.* **2000**, *65*, 5917–5925.
23. Krishnudu, K.; Krishna, P. R.; Mereyala, H. B. *Tetrahedron Lett.* **1996**, *37*, 6007–6010.
24. Grushin, V. V. *Organometallics* **2000**, *19*, 1888–1900.
25. The *cis*-dihydrodiol metabolites **1a**–**b** were obtained using *P. putida* F39/D under the biotransformation conditions previously reported.[2] Compounds **1c**–**k** were prepared according to previous reports.[19–21] Conventional heating reactions were performed according to Boyd's protocol.[5] Microwave reactions were performed in a commercially available monomode reactor (CEM Explorer). Reactions were carried out in 10 mL Pyrex vials sealed with septa and using magnetic stirring. *General procedure for Stille reaction using microwave heating*: To a solution of *cis*-dihydrodiol derivative (0.37 mmol) and tetrakis(triphenylphosphine) palladium (0) (63 mg, 0.055 mmol) in anhydrous THF (2 mL), allyltributyltin was added (0.12 mL, 0.40 mmol). The mixture was irradiated in a microwave at 90–120 °C and 200 W for 5–10 min in a sealed tube under a nitrogen atmosphere. Removal of the solvent and purification by flash chromatography on silica gel (EtOAc/hexanes) gave the cross-coupling product.
26. *Spectral data for selected compounds*: **2c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00 (dd, J_1 = 3.5 Hz, J_2 = 9.8 Hz, 1H), 5.88 (m, 1H), 5.84 (dd, J_1 = 4.4 Hz, J_2 = 8.6 Hz, 1H), 5.76 (m, 1H), 5.17 (d, J = 1.7 Hz, 1H), 5.13 (m, 1H), 4.68 (dd, J_1 = 3.9 Hz, J_2 = 8.6 Hz, 1H), 4.56 (d, J = 8.6 Hz, 1H), 3.00 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H) ppm; *Compound* **2e**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.10 (dt, J_1 = 1.6 Hz, J_2 = 5.4 Hz, 1H), 5.94 (d, J = 5.3 Hz, 1H), 5.81 (m, 1H), 5.75 (dd, J_1 = 3.0 Hz, J_2 = 10.0 Hz, 1H), 5.61 (m, 1H), 5.54 (d, J = 6.0 Hz, 1H), 5.14 (dd, J_1 = 1.6 Hz, J_2 = 8.6 Hz, 1H), 5.10 (d, J = 1.3 Hz, 1H), 2.91 (d, J = 8.0 Hz, 2H), 2.08 (s, 3H), 2.07 (s, 3H) ppm; *Compound* **2f**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84 (m, 1H), 5.62 (d, J = 4.3 Hz, 1H), 5.16 (dd, J_1 = 1.0 Hz, J_2 = 6.7 Hz, 1H), 5.11 (d, J = 1.0 Hz, 1H), 4.55 (d, J = 5.9 Hz, 1H), 4.36 (t, J = 6.5 Hz, 1H), 4.30 (m, 1H), 3.93 (dd, J_1 = 3.7 Hz, J_2 = 6.8 Hz, 1H), 2.97 (dd, J_1 = 6.4 Hz, J_2 = 16 Hz, 1H), 2.90 (dd, J_1 = 7.5 Hz, J_2 = 16 Hz, 1H), 2.71 (br s, 2H), 1.44 (s, 3H), 1.40 (s, 3H) ppm; *Compound* **2h**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.85 (m, 1H), 5.59 (s, 1H), 5.15 (dd, J_1 = 1.4 Hz, J_2 = 4.9 Hz, 1H), 5.12 (s, 1H), 4.53 (d, J = 6.4 Hz, 1H), 4.08 (m, 2H) 3.60 (t, J = 8.4 Hz, 1H), 2.96 (dd, J_1 = 6.2 Hz, J_2 = 16 Hz, 1H), 2.90 (dd, J_1 = 7.6 Hz, J_2 = 16 Hz, 1H), 1.52 (s, 3H), 1.41 (s, 3H) ppm; *Compound* **2i**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (m, 1H), 5.50 (d, J = 1.4 Hz, 1H), 5.14 (m, 1H), 5.10 (s, 1H), 4.53 (m, 2H), 4.39 (m, 1H), 3.60 (ddd, J_1 = 1.2 Hz, J_2 = 2.5 Hz, J_2 = 7.7 Hz, 1H), 2.90 (m, 1H), 2.74 (d, J = 7.1 Hz, 1H), 2.55 (d, J = 4.4 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H) ppm.