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Oxidative cleavage of unsaturated 1,2-diols using chiral lead-tetracarboxylates obtained by in situ metathesis

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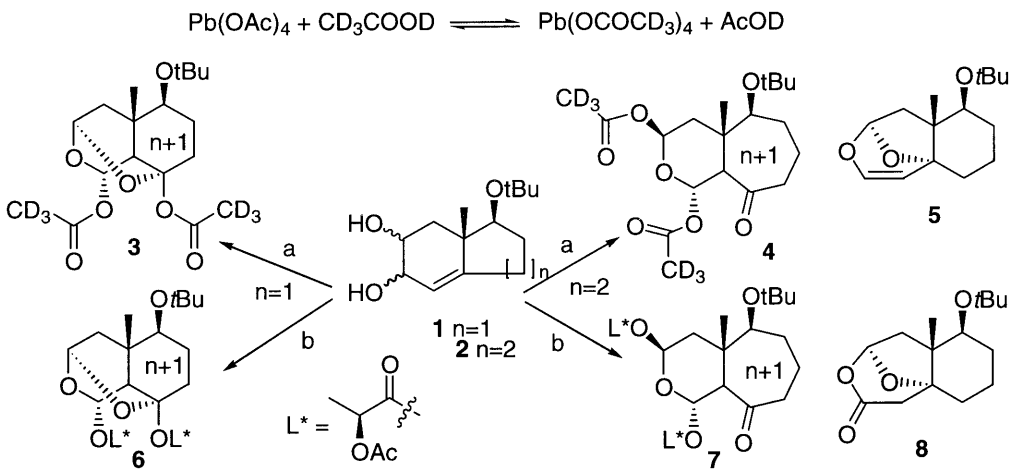
Abstract—A combination of an acetate metathesis/cascade transformations process, providing ring enlarged systems decorated with a chiral auxiliary, is presented. The use of a chiral carboxylic acid, such as (*S*)-2-acetoxypropionic acid, gives diastereomeric mixtures when performed in the racemic series, offering the possibility of a chemical resolution. © 2000 Published by Elsevier Science Ltd.

While designing strategies for the taxoid diterpene skeleton construction, a serendipitous discovery led to the development of a new 'cascade-type' ring-expansion/rearrangement methodology.[1] The utility of this methodology with regard to the synthesis of biologically active natural products was demonstrated by the large scale preparation of a conveniently functionalized taxoid C-ring precursor[2] which in turn was elaborated into the highly oxygenated taxoid ABC tricyclic system.[3] Exploring the solvent effect on the above mentioned transformations, mediated by $Pb(OAc)_4$, we examined a number of solvents compatible with the reagent used, namely benzene, trifluorotoluene, acetone, methylene chloride, chloroform, DME, DMF, THF and acetic acid. The product ratios and reaction rates were clearly dependent on solvent polarity and the observed solvent effect on the rate of cascade transformations can be rationalized by examining the proposed mechanism of this reaction sequence.[4] In this communication, we report examples of this methodology carried out in a chiral carboxylic solvent, ensuring high complexity but also enantiomeric purity in a single synthetic operation. During a preliminary study[5] we noticed that the use of deuterium labeled acetic acid led to the



Scheme 1. (a) $Pb(OAc)_4$, CD_3COOD, rt. (b) $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, rt.

Keywords: ring expansion; cascade transformations; acetate metathesis; chiral carboxylic solvents.

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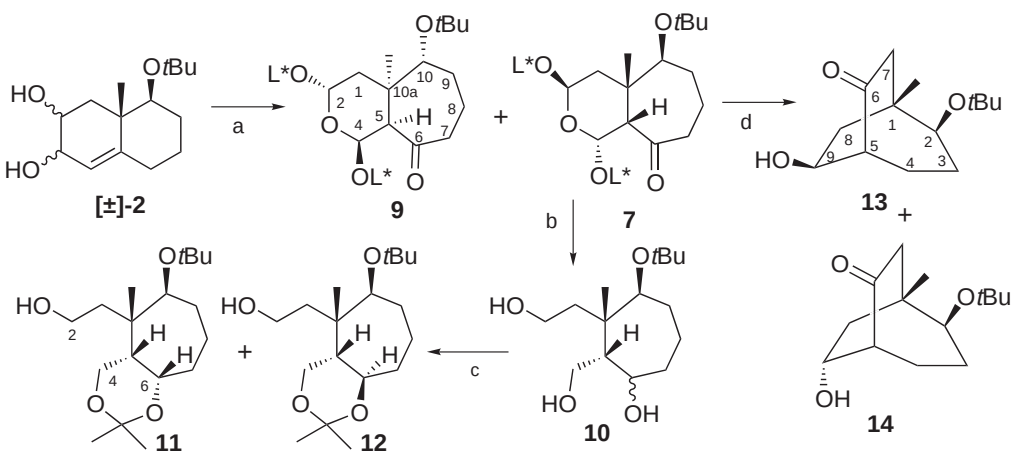
exclusive formation of CD_3-labeled compounds, indicating that metathesis[6] of the acetic acid by its labeled counterpart has occurred during the process. As portrayed in Scheme 1, room temperature treatment of the Hajos–Parrish ketone derived hydrindene diol **1** with 2 equiv. of lead tetraacetate in deuterated acetic acid (ca. 5 mL per mmol) afforded exclusively **3** ($[\alpha]_D$ −30, *c* 3.1, mp: 134–135°C, heptane–ether), while similar treatment of the Wieland–Miescher ketone derived unsaturated diol **2** afforded **4** (68%, $[\alpha]_D$ −64, *c* 1.8), along with the half cascade intermediate **5**[7] (5%) and a small amount of the tricyclic lactone **8** (11%, $[\alpha]_D$ +13, *c* 1.4), which presumably derives from **5**.

It was then of interest to investigate the applicability of this approach for the synthesis of chiral non-racemic cyclohexane and cycloheptane derivatives using in situ generated chiral lead carboxylates. We were thus interested in checking whether a chiral lead carboxylate could afford cascade transformations (modification of the ligands could influence reactivity) and ensure resolution, all in one synthetic operation. This would be of great synthetic use, especially for the Wieland–Miescher ketone derived diols of type **2**, as the enantiomeric excess obtained via the proline catalyzed Robinson annelation remains moderate.[8] To check the feasibility of this process and to gain familiarity with the proposed chemistry, the process was first tested on known optically pure unsaturated diols **1** and **2**. (*S*)-2-Acetoxypropionic acid ((*S*)-*O*-acetyl lactic acid) was found to be an optimal solvent for this process as it is liquid, it boils at a much higher temperature than acetic acid and it is easy to prepare on a large scale from commercially available inexpensive lactic acid.[9] The experiments undertaken with lead tetraacetate in the Hajos–Parrish series uniformly gave rise to the ring-enlarged acetal **6** as the sole detectable product. When treated with 2 equiv. of lead tetraacetate in (*S*)-2-acetoxypropionic acid (ca. 5 mL per mmol) under reduced pressure, **1** underwent cascade transformations in less than 10 h at room temperature to give **6** ($[\alpha]_D$ −35, *c* 1.8) in 85% isolated yield. Taking into account the high level of molecular complexity attained in a one-pot transformation, the yield is remarkably high (the only loss appeared to be due to the work-up conditions).

In the Wieland–Miescher series, proceeding as above, bis-lactyloxy acetal **7** ($[\alpha]_D$ −80, *c* 1.7) and lactone **8** were obtained in 70 and 11% yields, respectively. It was interesting to observe that the use of (*S*)-2-acetoxypropionic acid as solvent gave rise to a dramatic acceleration, furnishing a high isolated yield of **7** after only 1 h of stirring at room temperature.[10] The process passed the test successfully affording, in a single step, a ring expansion along with a functional reorganization and, above all, resolution (Scheme 2). Upon treatment with 2 equiv. of $Pb(OAc)_4$ in (*S*)-2-acetoxypropionic acid and proceeding as above, diol [±]-**2** gave, following chromatographic separation, **7** (36%) and **9** (34%, $[\alpha]_D$ −4, *c* 1.2) in 70% combined isolated yield, together with lactone **8** (8%).

The construction of the enantiomerically pure seven-membered ring segments **11** and **12** was then undertaken. Reduction of **7** (absolute configurations as depicted in Scheme 2) with $LiAlH_4$ in THF (room temperature, then reflux for 30 min) afforded the diastereomeric mixture of the corresponding cycloheptane-triols **10** (1:1 ratio, 99% isolated yield). Selective protection of the C-4, C-6 hydroxy groups as the acetonide was accomplished by treating the resulting triol in methylene chloride with anhydrous acetone and a catalytic amount of *p*TsOH under argon at room temperature (85%). Recrystallization from hexane precipitated most of the slower eluting *cis*-fused isomer **11** ($[\alpha]_D$ +33, *c* 0.9). The *trans*-fused acetonide **12** ($[\alpha]_D$ +31, *c* 1.2) was then separated on silica gel (methylene chloride–methanol, 98:2 as eluent). Following transformation of the free primary hydroxyl group at C-2, a chemoselective functionalization of the secondary hydroxyl group of **11** or **12** at C-6 using literature procedures should provide an easy access to optically homogeneous, polysubstituted cycloheptane derivatives. The bicyclo[3.2.2]nonane aldol derivatives **13** and **14** were easily obtained in one step from the *cis*-fused bicyclic derivative **7**, by dissolving the latter in methanol–water (8:1) and stirring the reaction mixture in the presence of K_2CO_3. After an overnight stirring at room temperature, a fused to bridged ring system interchange led to a diastereomeric mixture (nearly 1:1 ratio,



Scheme 2. (a) $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, rt. (b) $LiAlH_4$, THF, reflux. (c) Acetone, H^+. (d) K_2CO_3, $MeOH-H_2O$, rt.

87% yield) of bicyclic aldols **13** ($[\alpha]_D$ +92, *c* 1.1) and **14** ($[\alpha]_D$ +70, *c* 1.1), separated by chromatography on silica gel (elution with ethyl acetate–heptane–methanol, 1:1:0.01).

The results described above demonstrate the power of the lead tetraacetate mediated one-pot multi-stage transformation methodology for the rapid synthesis of complex molecules. Inexpensive (*S*)-2-acetoxypropionic acid proved compatible with the cascade transformations; the process offers the possibility of a chemical resolution, via chromatographic separation or recrystallization, when performed in the racemic series. So far, these promising results have a shortcoming: the use of a twofold excess of the toxic lead tetraacetate; we are currently engaged in further improvement of the scope and extension of this process to a catalytic system.[11] In all cases, structures and configuration of products were assigned by comprehensive spectral data; optical rotations were measured in chloroform and NMR spectra in $CDCl_3$.[12]

Acknowledgements

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6. It is well known that various lead(IV) carboxylates can be easily prepared by metathesis of the acetate with the corresponding carboxylic acid, the latter being used as solvent for the reaction. The acetic acid thus formed is removed under reduced pressure, thus shifting the equilibrium to the right. Bachman, G. B.; Wittman, J. W. *J. Org. Chem*. **1963**, *28*, 65–68.
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10. Using acetonitrile, trifluorotoluene or benzene as solvent the corresponding bis-acetoxy acetal required 50 h of stirring at room temperature for completion.
11. For the electrocatalytic oxidative cleavage of 1,2-diols by electrogenerated Pb(IV), see: Marken, F.; Squires, A. M.; Alden, J. A.; Compton, R. G.; Buston, J. E. H.; Moloney, M. G. *J. Phys. Chem. B* **1998**, *102*, 1186–1192.
12. Typical procedure: A dry flask was charged with 700 mg (2.92 mmol) of (±)-**2** and 2.7 g (6.1 mmol) of $Pb(OAc)_4$, vacuumed, flushed with argon and then again vacuumed for 1 h. (*S*)-2-acetoxypropionic acid (10 mL) was then added at room temperature and stirring continued for 30 min under argon and an additional 30 min under reduced pressure (ca. 4 mmHg). The reaction mixture was then diluted with ether (200 mL), washed with water (3×20 mL), 6N NaOH (3×10 mL) and water again (2×20 mL). The organic layer was dried over magnesium sulphate and the solvent evaporated under reduced pressure. The residue was purified on silica gel (toluene–ether 4:1) to yield 536 mg of **7** (36%), 506 mg of **9** (34%) along with 62 mg of lactone **8** (8%). Compound **7**: $[\alpha]_D$ −80 (*c* 1.7). IR (film): 2982, 2943, 1746, 1456, 1371, 1345, 1312, 1246, 1187, 1127, 1101, 1062, 1049, 989, 943, 910, 737 cm^{-1}. ^1H NMR (600 MHz): 1.14 (9H, s, *t*Bu), 1.30 (3H, s, Me-10a), 1.48 (3H, d, $J = 7.2$), 1.55 (3H, d, $J = 67.2$), 1.62 (1H, m, H-8α), 1.72 (1H, dt, $J = 4.3$, 14.9, H-9α), 1.84 (1H, dd, $J = 1.4$, 14.8, H-1β), 1.88 (1H, dd, $J = 4.2$, 14.8, H-1α), 1.93 (1H, m, H-8β), 2.00 (1H, dq, $J = 2.6$, 14.9, H-9β), 2.08 (3H, s, MeCO), 2.11 (3H, s, MeCO), 2.42 (1H, m, H-7), 2.54 (1H, m, H-7′), 2.93 (1H, d, $J = 3.4$, H-5), 2.95 (1H, d, $J = 8.9$, H-10), 4.92 (1H, q, $J = 7.2$), 5.08 (1H, q, $J = 7.2$), 6.30 (1H, d, $J = 3.4$, H-4), 6.47 (1H, dd, $J = 1.4$, 3.8, H-2). Diagnostic NOE's: {Me-10a}: H-4, H-1βeq., H-5, H-9βax; {H-4}: H-5, Me-10a; {H-10}: H1αax, H-8α; {H-5}: H-4, H7β, H-9β, Me-10a; {H-9β}: Me-10a, H-5, H-9α (NOE gem). ^{13}C NMR (75 MHz): 16.4 (MeCH), 16.7 (MeCH), 20.1 (Me-10a), 20.5 (CH_3CO), 20.6 (CH_3CO), 22.9 (C-8), 28.7 (*t*Bu), 30.5

(C-9), 35.0 (C-1), 37.6 (Cq-10a), 45.5 (C-7), 53.2 (C-5), 68.3 (C*H), 68.4 (C*H), 73.9 (Cq-*t*Bu), 80.0 (C-10), 88.8 (C-4), 93.1 (C-2), 168.8 (2×C, Me<u>C</u>O), 170.2 (Me<u>C</u>O), 170.4 (Me<u>C</u>O), 208.7 (C-6). ESI-MS (MeOH): 537 ($[MNa]^+$, 100), 553 ($[MK]^+$, 12), 1051 ($[2MNa]^+$, 20). Compound **9**: $[\alpha]_D$ −4 (*c* 1.2). IR (film): 2975, 2941, 1747, 1716, 1583, 1455, 1372, 1344, 1303, 1237, 1189, 1174, 1127, 1097, 1049, 994, 941, 736 cm^{-1}. ^1H NMR (600 MHz): 1.13 (9H, s), 1.21–2.59 (9H, m), 1.29 (3H, s), 1.49 (3H, d, $J = 6.9$), 1.53 (3H, d, $J = 6.9$), 2.09 (3H, s), 2.13 (3H, s), 2.96 (1H, t, $J = 3.4$), 5.07 (1H, q, $J = 6.9$), 5.18 (1H, q, $J = 6.9$), 6.33 (1H, d, $J = 3.2$), 6.47 (1H, bs). ^{13}C NMR (75 MHz): 16.7, 16.8, 20.5 (3C), 23.1, 28.8 (3C), 30.5, 35.1, 37.4, 45.6, 53.1, 68.5 (2C), 74.0, 80.2, 89.2, 93.7, 168.6, 168.9, 170.1, 170.5, 208.7. CI-MS: 532 ($[M+NH_4]^+$, 97), 460 (47), 400 (100), 383 (6).