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Synthesis of cyclopentane building blocks via an intramolecular C–H insertion reaction of a chiral pool derived α-diazo-γ-hydroxy-β-ketosulfone

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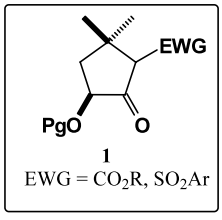
Abstract—A highly functionalized cyclopentanone building block **13** was prepared by a facile Rh-catalyzed intramolecular C–H insertion reaction of an enantiopure α-diazo-γ-hydroxy-β-ketosulfone **12**, in turn derived from an α-hydroxy acid **2**. A cyclic γ-hydroxy vinyl sulfone **16** was also prepared from **13**.

In a program directed towards the synthesis of triquinane skeletons,[1] we identified the cyclopentanone derivative **1** as a key building block. By virtue of its dense functionalization and an embedded *gem*-dimethyl substitution, **1** promised to serve as a common intermediate for the synthesis of various sesquiterpenes and related natural products. However, its contiguous substitution pattern including the presence of chiral centers, made its synthesis a vastly challenging task. Not surprisingly, several attempts at its synthesis via classical Dieckmann-type cyclization reactions failed.[2] Still in pursuit, our attention was drawn to the large number of reports on five-membered ring construction via catalyzed intramolecular C–H insertion reactions of α-diazocarbonyl compounds.[3] Among the catalysts used for these reactions, Rh-salts are the overwhelming favorites, although examples of Cu-catalyzed intramolecular C–H insertion reactions leading to five-membered rings are also known.[4] Both carbocyclic and heterocyclic five-membered rings have been synthesized in this way.[3] Non-racemic syntheses of these ring systems are also known either via the use of chirally modified Rh-catalysts or by using enantiopure diazocarbonyl substrates. There are several reports on the synthesis of cyclopentane derivatives using this regime, although examples of the non-racemic variety are less documented.[3c,5] Intramolecular C–H insertion reactions, in view of their mild and neutral reaction conditions and high functional group tolerance, appeared to be an attractive strategy for the synthesis of a highly functionalized cyclopentanone derivative such as **1**. Our success towards this end is described in this letter.



1
EWG = CO_2R, SO_2Ar

The *O*-acetyl α-diazo-β-ketosulfone **6** was initially chosen as the substrate for the C–H insertion reaction towards **1**. The choice of the isobutyl side chain in **6** was of critical importance. Taber et al. have shown that for a series of α-diazoketones, intramolecular C–H insertion reactions usually occur at the γ-carbon to produce five-membered rings and that they occur preferentially at the γ-carbon which is more substituted (2° > 1°).[6] Accordingly, in **6**, we chose an isobutyl side chain since it would provide a highly favorable methine carbon (2°) as the insertion terminus leading to facile five-membered ring construction and, in the process, would also set up the *gem*-dimethyl substitution pattern in **1**. The synthesis of **6** is shown in Scheme 1. Starting from the α-hydroxy acid **2** (readily prepared from *L*-leucine)[7] which via its acetate **3**,[8] and the corresponding diazoketone **4** (77%), was converted in two easy steps to the γ-acetoxy-β-ketosulfone **5** in a good overall yield.[9,10] Diazo-transfer on **5** with TsN_3 (Et_3N, CH_2Cl_2,

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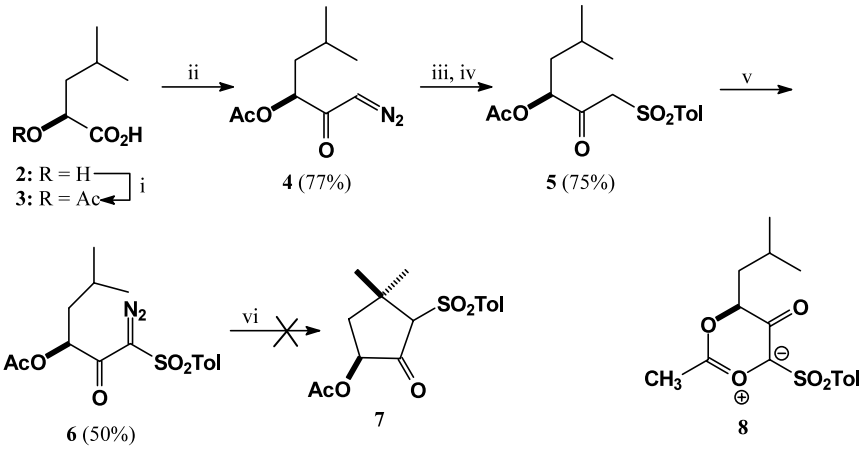
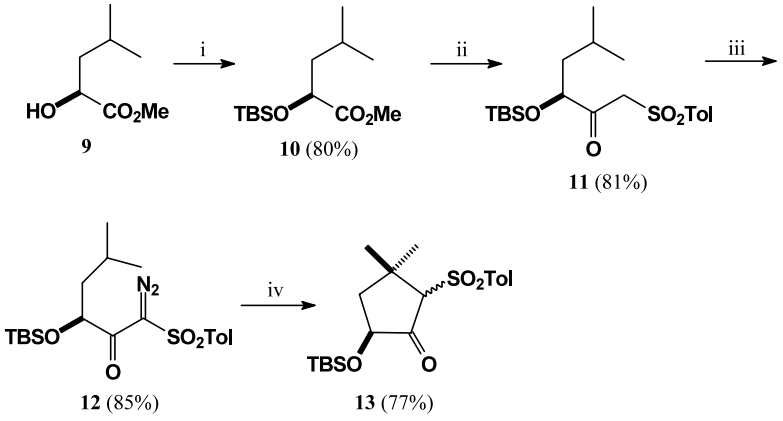


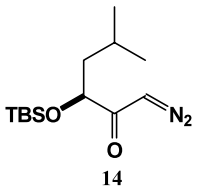
Scheme 1. *Reagents and conditions*: (i) CH_3COCl, rt; (ii) $SOCl_2$, benzene, reflux then excess CH_2N_2, ether, 0°C; (iii) 48% HBr, ether, 0°C; (iv) $NaSO_2Tol$, DMF, rt; (v) TsN_3, Et_3N, CH_2Cl_2, rt; (vi) 1% $Rh_2(OAc)_4$.

rt)[11] then gave **6** in moderate yield. However, repeated attempts at the $Rh_2(OAc)_4$ catalyzed intramolecular C–H insertion reaction in **6** failed to provide the desired cyclopentanone **7** under a variety of conditions. The use of Cu-catalysts, e.g. $Cu(acac)_2$ or Cu_2O also resulted in failures. In all these attempts, although the substrate was fully consumed, no isolable products could be identified by TLC analysis of the reaction mixture. We attributed these failures to the presence of the neighboring acetate functionality in **6** which probably engaged the incipient carbenoid into intramolecular ylide formation (leading to **8**), thereby suppressing the C–H insertion pathway. That ylide formation can effectively compete with C–H insertion reactions in Rh-catalyzed reactions of suitably disposed α-diazoketones has been reported by others.[12]

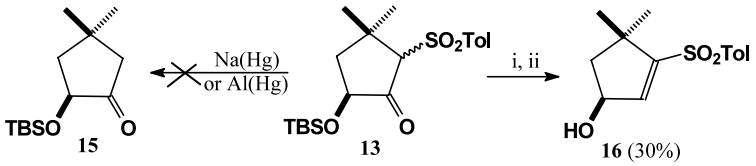
The acetate protecting group was hence discarded and the non-interfering OTBS group chosen instead. Others have shown that in intramolecular C–H insertion reactions of δ-hydroxy-α-diazo-β-keto esters, an OTBS protecting group effectively blocks competing oxonium ylide formation.[5f] The synthesis of the OTBS protected α-diazo-β-ketosulfone **12** is shown in Scheme 2. Thus, the α-hydroxy methyl ester **9**[13] was first protected as the TBS ether to give **10** (80%) and the latter reacted with α,α-dilithio methyl tolyl sulfone (CH_3SO_2Tol, 2 equiv. *n*-BuLi, THF, 0°C)[14] to give the OTBS substituted β-ketosulfone **11** in good yield. Diazo-transfer reaction onto **11**, as before with TsN_3,[11] then produced the key α-diazo-β-ketosulfone **12** in 85% yield. Most gratifyingly, exposure of **12** to 1% $Rh_2(OAc)_4$ (CH_2Cl_2, rt, slow addition of the substrate) smoothly gave rise to the desired cyclopentanone derivative **13** (77%) as a mixture of diastereomers (80/20 by NMR). That the C–H insertion reaction had taken place at the side chain methine carbon in **12**, i.e. its isopropyl group had been transformed into a *gem*-dimethyl substituent in **13**, was clearly evident from the ^1H NMR analysis of these two compounds. Thus, the signal for the methine proton of **12** (δ 1.52–1.70, m) was absent in **13**. Moreover, the pair of three proton doublets at δ 0.83 and 0.85 in **12** due to its two terminal methyl groups were replaced by a pair of three proton singlets (at δ 0.80 and 0.83 in the major diastereomer) in **13** due to the *gem*-dimethyl substitution pattern.



Scheme 2. *Reagents and conditions*: (i) TBS-Cl, cat. imidazole, Et_3N, CH_2Cl_2, rt; (ii) CH_3SO_2Tol, 2 equiv. *n*-BuLi, THF, –78 to 0°C; (iii) TsN_3, Et_3N, CH_2Cl_2, rt; (iv) 1% $Rh_2(OAc)_4$, CH_2Cl_2, rt.



14



15 13 16 (30%)

Scheme 3. *Reagents and conditions*: (i) $NaBH_4$, MeOH–THF, 0°C; (ii) MsCl, py, rt.

In the course of this investigation, we also examined the Rh-catalyzed reaction of the diazoketone **14** which lacks the sulfone group present in **12**. However, only dimerization and decomposition products were obtained in this case. Thus, appropriate pairing of the reaction centers, i.e. a methine insertion terminus and a highly electrophilic carbenoid carbon, appears to be essential for the C–H insertion reaction to take place successfully.

With **13** in hand, we briefly examined some of its chemistry (Scheme 3). Reductive desulfonation to the α-hydroxy ketone **15** was first attempted since the latter appeared to be an ideal precursor to a number of novel C_2-symmetric cyclic diols. However, treatment of **13** with Na(Hg) or Al(Hg) invariably led to decomposition products. We are currently looking at milder methods to carry out this desulfonation reaction. However, borohydride reduction of **13** followed by elimination with MsCl/Py successfully gave the novel cyclic γ-hydroxy vinyl sulfone **16** (the TBS protecting group was lost in the process) in a low yield (unoptimized). Acyclic γ-hydroxy vinyl sulfones have found considerable use in asymmetric synthesis.[15] The cyclic variety **16** and its congeners also hold much promise towards similar usage.

In summary, we have described a facile synthetic entry into highly functionalized cyclopentane derivatives via an intramolecular C–H insertion strategy. This strategy, we believe, should also find use in the synthesis of other types of non-racemic cyclopentane derivatives.

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10. Representative physical data for selected compounds. **4**: yellow oil; $[\alpha]_D^{20}$ −56.1 (*c* 5.5, $CHCl_3$); IR (neat) 2100, 1735, 1635, 1350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90–1.00 (m, 6H), 1.50–1.80 (m, 3H), 2.12 (s, 3H), 5.08 (dd, 1H, $J=4.0$, 8.0 Hz), 5.39 (s, 1H). Anal. calcd for $C_9H_{14}N_2O_3$: C, 54.54; H, 7.04; N, 14.14. Found: C, 54.18; H, 7.03; N, 13.83%. **5**: colorless oil; $[\alpha]_D^{20}$ −23.9 (*c* 4.2, $CHCl_3$); IR (neat) 1720, 1595, 1450 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.92–1.00 (m, 6H), 1.56–1.80 (m, 3H), 2.14 (s, 3H), 2.46 (s, 3H), 4.12–4.48 (m, 2H), 5.18 (dd, 1H, $J=5.0$, 8.0 Hz), 7.40 (d, 2H, $J=8.0$ Hz), 7.86 (d, 2H, $J=8.0$ Hz). Anal. calcd for $C_{16}H_{22}O_5S$: C, 58.89; H, 6.74. Found: C, 58.50; H, 6.94%. **6**: yellow oil; $[\alpha]_D^{20}$ +38.8 (*c* 0.4, $CHCl_3$); IR (neat) 2100, 1745, 1665, 1595, 1365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, 6H, $J=6.6$ Hz), 1.60–1.80 (m, 3H), 2.06 (s, 3H), 2.45 (s, 3H), 5.36 (dd, 1H, $J=4.0$, 9.6 Hz), 7.37 (d, 2H, $J=8.3$ Hz), 7.89 (d, 2H, $J=8.3$ Hz). Anal. calcd for $C_{16}H_{20}N_2O_5S$: C, 54.54; H, 5.68; N, 7.95. Found: C, 54.62; H, 5.65; N, 7.91%. **11**: colorless oil: $[\alpha]_D^{27}$ −8.0 (*c* 1.4, $CHCl_3$); IR (neat) 2950, 2850, 1720, 1590, 1460, 1320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.85 (d, 3H, $J=3.0$ Hz), 0.87 (d, 3H, $J=3.0$ Hz), 0.89 (s, 9H), 1.30–1.45 (m, 2H), 1.45–1.65 (m, 1H), 2.44 (s, 3H), 4.11 (dd, 1H, $J=6.2$, 7.3 Hz), 4.22 (d, 1H, $J=15.3$ Hz), 4.47 (d, 1H, $J=15.3$ Hz), 7.36 (d, 2H, $J=8.4$ Hz), 7.81 (d, 2H, $J=8.4$ Hz). Anal. calcd for $C_{20}H_{34}O_4SSi$: C, 60.30; H, 8.54. Found: C, 60.22; H, 8.60%. **12**: yellow oil; $[\alpha]_D^{20}$ −5.9 (*c* 3.8, $CHCl_3$); IR (neat) 2920, 2840, 2100, 1710, 1590, 1450, 1340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.09 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 0.85 (d, 3H, $J=6.0$ Hz), 0.88 (d, 3H, $J=6.0$ Hz), 1.20–1.50 (m, 2H), 1.52–1.70 (m, 1H), 2.44 (s, 3H), 4.16 (dd, 1H, $J=6.0$, 8.0 Hz), 7.33 (d, 2H, $J=8.1$ Hz), 7.91 (d, 2H, $J=8.1$ Hz). Anal. calcd for $C_{20}H_{32}N_2O_4SSi$: C, 56.60; H, 7.54; N, 6.60. Found: C, 56.68; H, 7.50; N, 6.08%. **13**: colorless oil; IR ($CHCl_3$) 3000, 1750, 1590, 1460, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.77 (s, 9H), 0.80 (s, 3H), 0.83 (s, 3H), 2.16 (dd, 1H, $J=8.5$, 12.5 Hz), 2.28–2.38 (m, 1H), 2.36 (s, 3H), 3.47 (br s, 1H), 4.24 (dd, 1H, $J=8.5$, 3.0 Hz), 7.22–7.26 (m, 2H), 7.71 (d, 2H, $J=8.0$ Hz). Anal. calcd for $C_{20}H_{32}O_4SSi$: C, 60.60; H, 8.08. Found: C, 60.83; H, 7.78%.

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