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Annulation of 3-methylcyclopentenone onto a cyclopentenol double bond by intramolecular Pauson–Khand reaction

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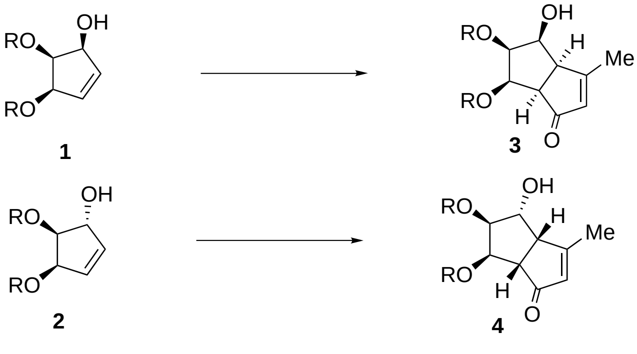
Abstract—A procedure for regio- and diastereocontrolled annulation of a 3-methylcyclopentenone moiety on a cyclopentenol double bond has been developed by employing the Pauson–Khand reaction in the presence of a promoter having reductive potential. During the examination, a novel substrate specific 3-hydroxycyclopentanone formation reaction was also discovered.

The Pauson–Khand reaction is an efficient and convenient tool for the construction of a cyclopentenone unit by combination of an alkyne, an olefin, and carbon monoxide from dicobalt octacarbonyl.[1] The reaction, however, does not exhibit regioselectivity to yield a regioisomeric mixture of cyclopentenones when unsymmetrical substrates are used. Although an intramolecular version of this reaction allows regiocontrol, it is limited to the generation of particular regioisomeric products. In relation to our recent project, we encountered a difficulty in the diastereocontrolled introduction of a 3-methylcyclopentenone moiety on the cyclopentenol double bond. In order to solve this problem, we investigated the construction of 3-methylcyclopentenone on the double bond of two isomeric dioxygenated cyclopentenols, **1** and **2**, to yield the corresponding isomeric diquinane derivatives **3** and **4** by employing the intramolecular Pauson–Khand reaction (Scheme 1).

Since the cyclopentenone moiety of both **3** and **4** resides on the same side to the hydroxy functionality, it is most convenient to utilize the hydroxy functionality as a handle for the regio- and diastereocontrol for the three-carbon annelation. Fortunately, there were some precedents[2] exhibiting reductive cleavage of the propargyl ether bond during the intramolecular Pauson–Khand reaction of certain allyl propargyl ethers giving rise to 3-methylcyclopentenone derivatives though a minor component. We, therefore, sought the conditions that would allow exclusive generation of the annelation products **3** and **4** under Pauson–Khand conditions. In this paper, we report the directed synthesis of two pairs of diastereomeric diquinane derivatives carrying a 3-methylcyclopentenone moiety and the fortuitous finding of substrate specific 3-hydroxylation reaction under Pauson–Khand conditions to yield triquinane structures having a 3-hydroxycyclopentane moiety.

We prepared four enyne substrates, two *syn*-dialkoxy derivatives **11a**,**b** and two *anti*-dialkoxy derivatives **12a**,**b** starting from cyclopentene[3] **5** as a common starting material. Thus, **5** was dihydroxylated diastereoselectively to give diol **6** from which two *O*-protected compounds, acetonide **7a** and di-MOM ether **7b**, were prepared. On catalytic hydrogenolysis, both gave the corresponding cylopentenols **8a**,**b** (Scheme 2).

To obtain *syn*-substrate **11a**,**b**, **8a**,**b** were oxidized with a sulfur trioxide–pyridine complex in dimethyl sulfoxide (DMSO) containing triethylamine[4] to give cyclopentenones **9a**,**b** in one-step through concurrent oxidation



Scheme 1.

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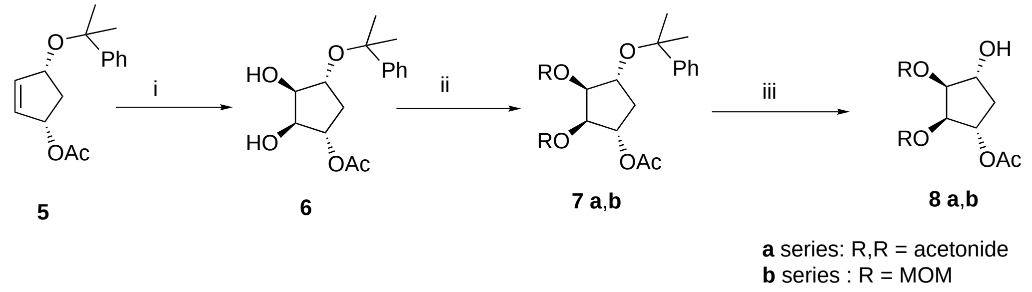
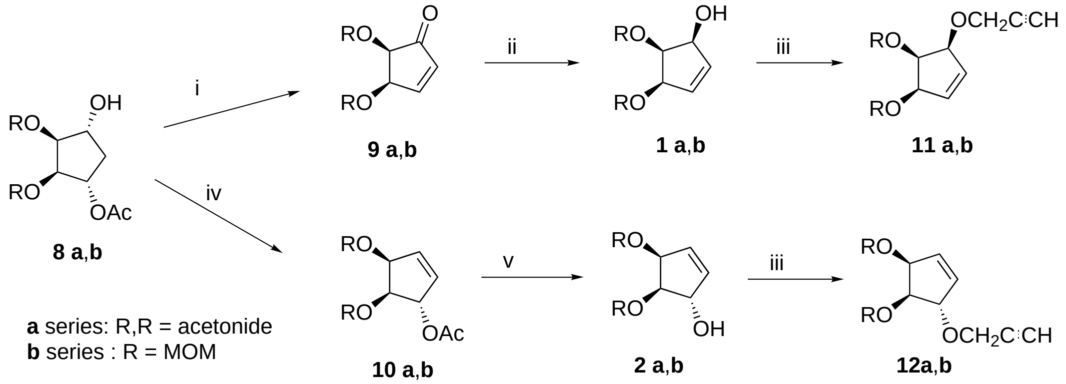


Scheme 2. *Reagents and conditions*: (i) OsO_4 (cat.), NMO, aq. THF (93%); (ii) for **a**: 2,2-dimethoxypropane, PPTS (cat.), CH_2Cl_2, rt, (96%); for **b**: MOM-Cl, *i*-Pr_2EtNH, CH_2Cl_2, rt (97%); (iii) H_2, 10% Pd-C, $CHCl_3$ (cat.), AcOEt (97% for **a**; 94% for **b**).

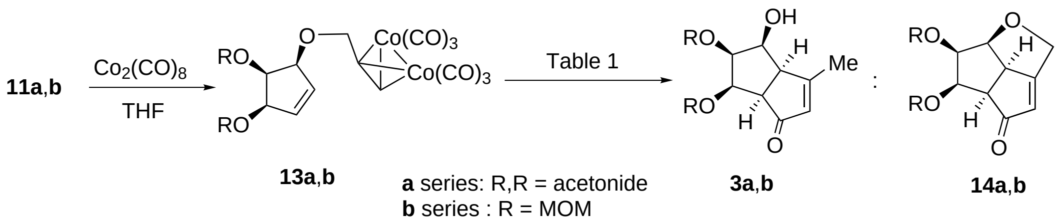
and elimination. Reduction of **9a**,**b** with sodium borohydride in the presence of cerium(III) chloride afforded diastereoselectively 1,2-reduction products **1a**,**b** which were transformed into the *syn*-substrates **11a**,**b** on reaction with propargyl bromide under standard conditions. On the other hand, to obtain the *anti*-substrates, **12a**,**b**, **8a**,**b** were treated with benzoic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to initiate dehydration[5] to yield *anti*-acetates **10a**,**b**. Interestingly, the dehydration of the acetonide **8a** under Mitsunobu conditions did not proceed neatly in the absence of benzoic acid though dehydration of the di-MOM ether-**8b** proceeded in the absence of the acid. On sequential methanolysis and *O*-alkylation, **10a**,**b** afforded the *anti*-substrates **12a**,**b** via cyclopentenols **2a**,**b** (Scheme 3).

The Pauson–Khand reaction of **11a**,**b** having *syn*-configuration was first examined. Treatment with **11a**,**b** with dicobalt octacarbonyl afforded the stable complexes **13a**,**b** in yields of 94 and 100%. The complexes were stirred in an appropriate solvent in the presence of one of five initiators. When the reaction was carried out in the presence of trimethylamine *N*-oxide[2c] (TMANO), a normal-type Pauson–Khand reaction occurred to give the tricyclic enones **14a**,**b** without formation of the bicyclic 3-methylenones **3a**,**b**. However, when methyl phenyl sulfide[6] or DMSO[7] was used as an initiator, the expected reductive cleavage occurred to give the bicyclic 3-methylenones **3a**,**b** with normal-type products **14a**,**b**. Exclusive formation of the bicyclic products **3a**,**b** was attained in the presence of either cyclohexylamine[2d] or ammonium hydroxide.[2d] Although the yields of the bicyclic products were not high, the present method may be of practical use owing to its simplicity and to its regio- and diastereocontrol (Scheme 4, Table 1).

A similar result was obtained in the reactions of the complex **15a**,**b** obtained in yields of 99 and 85% from **12a**,**b** having *anti*-configuration with respect to the gen-



Scheme 3. *Reagents and conditions*: (i) SO_3–pyridine complex, DMSO–Et_3N, rt (84% for **a**; 56% for **b**); (ii) $NaBH_4$, $CeCl_3$–$7H_2O$, MeOH, −20°C (84% for **a**; 82% for **b**); (iii) NaH, propargyl bromide, THF, −20°C (83% for **11a**; 83% for **11b**; 72% for **12a**; 92% for **12b**); (iv) benzoic acid, PPh_3, DIAD, THF, rt; (v) K_2CO_3, MeOH, rt (71% from **8a**; 74% from **8b**).



Scheme 4.

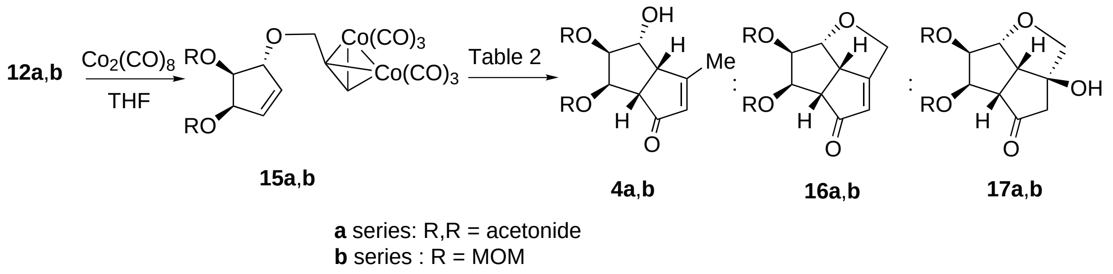
Table 1. Pauson–Khand reaction of the *syn*-substrates **13a**,**b**

Entry	**13**	Additive	Solvent	Temp. (°C)	Time (h)	**3** (%)	**14** (%)
1	**13a**	TMANO[a]	THF	−20 to rt	12	**3a** (0)	**14a** (39)
2	**13b**	TMANO[a]	THF	−20 to rt	12	**3b** (0)	**14b** (56)
3	**13a**	PhSMe[b]	$(CH_2Cl)_2$	Reflux	0.3	**3a** (0)	**14a** (2)
4	**13b**	PhSMe[b]	$(CH_2Cl)_2$	Reflux	0.3	**3b** (12)[c]	**14b** (39)[c]
5	**13a**	DMSO[d]	Benzene	Reflux	1.2	**3a** (10)[c]	**14a** (23)[c]
6	**13b**	DMSO[d]	Benzene	Reflux	2	**3b** (0)	**14b** (32)
7	**13a**	*c*-Hex-NH_2[b]	$(CH_2Cl)_2$	Reflux	2	**3a** (45)	**14a** (0)
8	**13b**	*c*-Hex-NH_2[b]	$(CH_2Cl)_2$	Reflux	0.3	**3b** (40)	**14b** (0)
9	**13a**	NH_4OH[e]	Dioxane	Reflux	1	**3a** (20)	**14a** (0)
10	**13b**	NH_4OH[e]	Dioxane	Reflux	1	**3b** (20)	**14b** (0)

[a] 3 equiv. were used.
[b] 3.5 equiv. were used.
[c] Obtained as an inseparable mixture.
[d] 6 equiv. were used.
[e] 30% NH_4OH–dioxane (3:1 v/v) was used.

eration of the 3-methylenones **4a**,**b**. Thus, reaction of **12a**,**b** in the presence of DMSO or the primary amines furnished the bicyclic 3-methylenones **4a**,**b** in acceptable yields as for the *syn*-counterparts. However, the reaction in the presence of TMANO anticipated to bring about a normal-type transformation did not furnish the expected tricyclic enones **16a**,**b** at all, but produced their hydration products, tricyclic 3-hydroxycyclopentanones **17a**,**b**, instead, in acceptable yields. A much better yield of the acetonide **17a** was obtained when 4-methylmorphorine *N*-oxide[8] (NMO) in place of TMANO was used. Since only one precedent [9] has been reported for the generation of a 3-hydroxylation product in the Pauson–Khand reaction as a minor component, the present observation leading to exclusive generation of the 3-hydroxylated products **17a**,**b** is noteworthy (Scheme 5, Table 2).

The observed unexpected diastereomer-dependent hydroxylation reaction under Pauson–Khand condi-

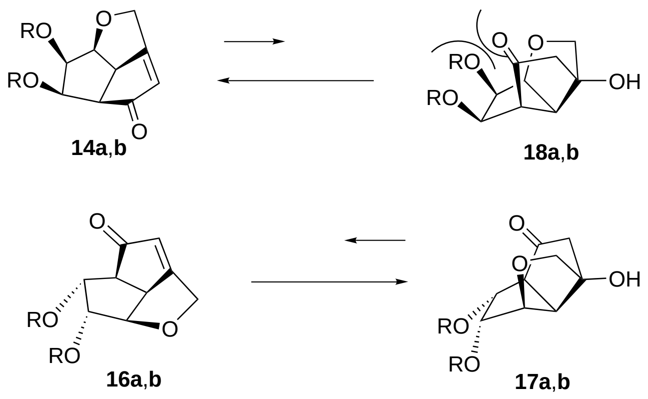


Scheme 5.

Table 2. Pauson–Khand reaction of the *anti*-substrates **15a**,**b**

Entry	**15**	Additive	Solvent	Temp. (°C)	Time (h)	**4** (%)	**16** (%)	**17** (%)
1	**15a**	TMANO[a]	THF	−20 to rt	14	**4a** (0)	**16a** (0)	**17a** (55)
2	**15b**	TMANO[a]	THF	−20 to rt	14	**4b** (0)	**16b** (0)	**17b** (40)
3	**15a**	NMO[b]	CH_2Cl_2	−20 to rt	14	**4a** (0)	**16a** (0)	**17a** (70)
4	**15a**	NMO[b]	CH_2Cl_2	−20 to rt	14	**4b** (0)	**16b** (0)	**17b** (36)
5	**15a**	PhSMe[c]	$(CH_2Cl)_2$	Reflux	0.3	**4a** (26)	**16a**(0)	**17a** (?)
6	**15b**	PhSMe[c]	$(CH_2Cl)_2$	Reflux	0.3	**4b** (17)	**16b**(0)	**17b** (0)
7	**15a**	DMSO[d]	Benzene	Reflux	1.2	**4a** (26)	**16a** (0)	**17a** (0)
8	**15b**	DMSO[d]	Benzene	Reflux	0.5	**4b** (90)	**16b** (0)	**17b** (0)
9	**15a**	*c*-Hex-NH_2[c]	$(CH_2Cl)_2$	Reflux	2	**4a** (21)	**16a** (0)	**17a** (0)
10	**15b**	*c*-Hex-NH_2[c]	$(CH_2Cl)_2$	Reflux	0.3	**4b** (45)	**16b** (0)	**17b** (0)
11	**15a**	NH_4OH[e]	Dioxane	Reflux	0.3	**4a** (45)	**16a** (0)	**17a** (0)
12	**15b**	NH_4OH[e]	Dioxane	Reflux	0.3	**4b** (42)	**16b** (0)	**17b** (0)

[a] 3 equiv. were used.
[b] 10 equiv. were used.
[c] 3.5 equiv. were used.
[d] 6 equiv. were used.
[e] 30% NH_4OH–dioxane (3:1 v/v) was used.



Scheme 6.

tions may be explained by a model examination though the actual hydration mechanism remains uncertain. As shown, hydration of the *syn*-tricyclic enones **3a**,**b** relieves the angle strain, but suffers from considerable nonbonding steric interaction to generate 3-hydroxyketones **18a**,**b**. The hydration of the diastereomeric *anti*-enones **4a**,**b** also relieves the angle strain, but suffers from non-bonding interaction to a less extent to produce 3-hydroxyketones **17a**,**b** (Scheme 6).

In conclusion, we have achieved our intention to construct a 3-methylcyclopentenone moiety regio- and diastereoselectively on the double bond of a cyclopentenol using two model compounds in the presence of an appropriate promoter. Utilization of the present results for the diastereocontrolled synthesis of natural products is presently under investigation.

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