Pergamon

Tetrahedron Letters 42 (2001) 231–234

TETRAHEDRON LETTERS

An expeditious construction of polycyclic ketals: synthesis of fused seven-membered rings and substituted naphthalenes

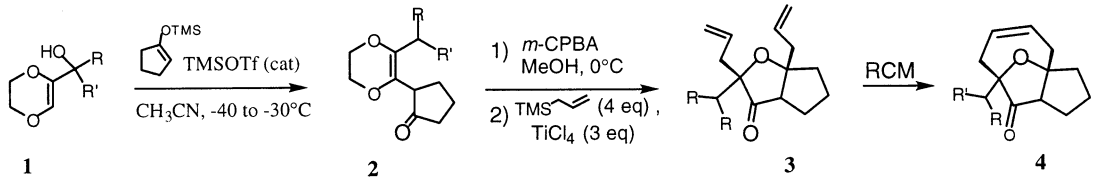
Issam Hanna,[a,*] Valérie Michaut[a] and Louis Ricard[b]

[a]*Laboratoire de Synthèse Organique associé au CNRS, F-91128 Palaiseau, France*
[b]*Laboratoire 'Hétéroéléments et Coordination' associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau, France*

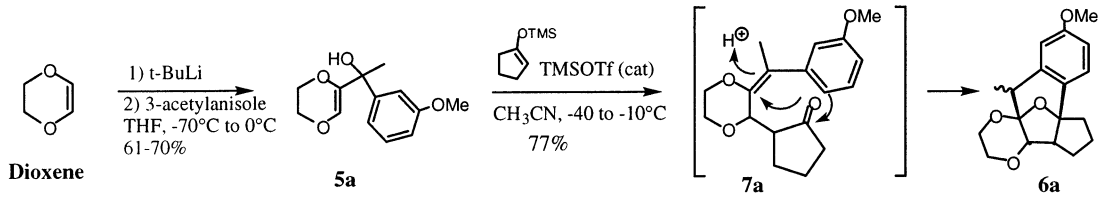
Received 9 October 2000; accepted 25 October 2000

Abstract—Treatment of allylic alcohols **5**, easily prepared from dioxene and methoxyacetophenones, with 1-(trimethylsilyloxy)cyclopentene in the presence of a catalytic amount of TMSOTf in acetonitrile, afforded a polycyclic acetal **6** by domino nucleophilic substitution, annulation and intramolecular Friedel–Crafts alkylation reaction sequence. Acid-mediated cleavage of the acetal moiety led to fused seven-membered carbocyclic rings or to substituted naphthalenes.

The development of reactions that efficiently generate polycyclic molecules from easily accessible starting materials continues to be an important trend in organic synthesis. For this purpose, domino reactions offer the advantage of executing multistep transformations without intermediate workup and therefore can be applied to the one-pot synthesis of polycyclic ring systems.[1] In recent reports, we have described the behaviour of allylic alcohols **1**, readily prepared by the addition of dioxenyllithium to ketones and aldehydes, towards nucleophilic displacement reactions in the presence of Lewis acids.[2] For instance, **1** reacts with various silyl enol ether such as 1-(trimethylsilyloxy)cyclopentene in the presence of a catalytic amount of trimethylsilyltrifluorosulfonate (TMSOTf) in acetonitrile to afford 2,3-disubstituted 1,4-dioxenes **2** in high yields (Scheme 1).[2b] Oxidation of **2** with *m*-chloroperbenzoic acid in methanol followed by nucleophilic addition of allyltrimethylsilane in the presence of $TiCl_4$ afforded dienes **3**, which have been converted to oxabicyclo[4.2.1] nonenes **4** in excellent yield by an olefin ring-closing metathesis reaction.[2c] We have found, and now report that a nucleophilic substitution reaction at allylic alcohols **5** bearing an aromatic substituent such as a



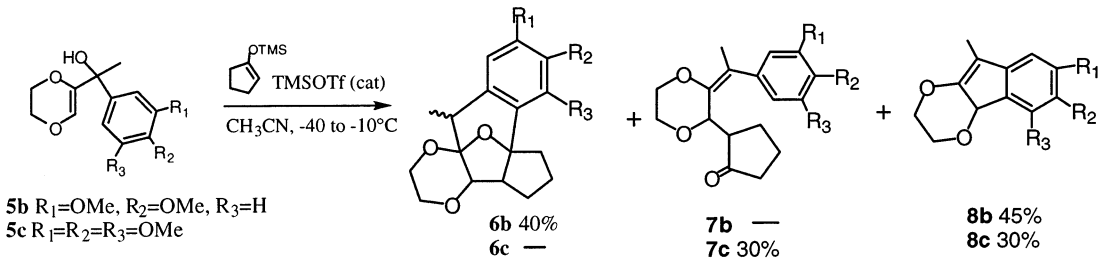
Scheme 1.



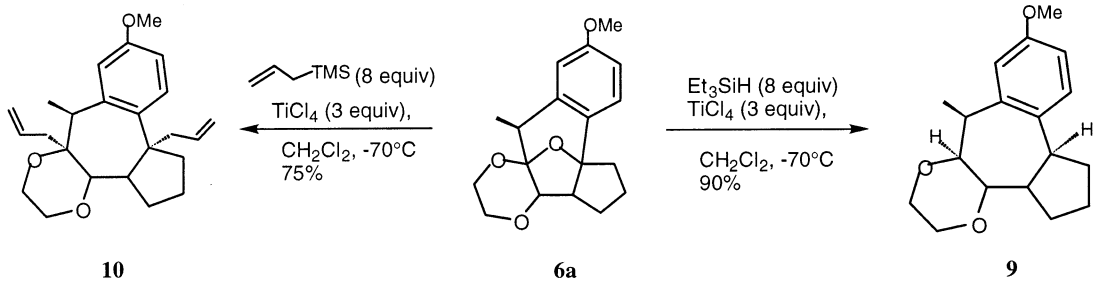
Scheme 2.

* Corresponding author. Fax: +33 1 69 33 30 10; e-mail: hanna@poly.polytechnique.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(00)01906-7



Scheme 3.



Scheme 4.

methoxyphenyl group gave, instead of **2**, a polycyclic acetal **6** by a triple-domino reaction.

Allylic alcohols **5** were readily prepared by addition of dioxenyllithium to corresponding acetophenones.[3] Treatment of **5a** with 1-(trimethylsilyloxy)cyclopentene (1.5 equiv.) in the presence of a catalytic amount (10 mol%) of TMSOTf in acetonitrile at −40 to −10°C led to the pentacyclic ketal **6a**[4] as a mixture of two diastereoisomers (2:1 ratio) separated by flash column chromatography in 77% combined yield (Scheme 2). These isomers only differ in the configuration of the benzylic carbon bearing the methyl group. The structural assignment for **6a** was based on its spectral data and was further confirmed by an X-ray crystal structure determination of acetal opened derivatives (Scheme 2).

The unexpected formation of this novel pentacyclic ring system can be rationalized as indicated in Scheme 2. We assume that Lewis acid-catalyzed nucleophilic substitution of the silyl enol ether at allylic alcohol **5a** occurs first providing **7a**. The protonation of the exocyclic double bond in **7a** initiates cyclization and leads to a tertiary carbocation which undergoes an intramolecular Friedel–Crafts alkylation.[5] This final step is undeniably assisted by the electron-donating methoxy group. In fact, in the absence of this group, the reaction is stopped at the cyclopentanone stage in agreement with the results of our previous investigations.[2]

Under the same reaction conditions, allylic alcohol **5b** afforded the same pentacyclic structure **6b** as above, albeit in lower yield (40%), along with the indene derivative **8b** (45%). In contrast, the presence of a third methoxy group in **5c** totally inhibited the aromatic electrophilic substitution and gave rise to cyclopentanone **7c** and indene **8c** in equal amounts (Scheme 3). As anticipated, when the reaction was carried out in the absence of an external nucleophile (e.g. the silyl enol ether), the indene derivative **8** was isolated as the sole product in nearly quantitative yield.

We next investigated the feasibility of the cleavage of the ether bond in the [3.2.1]oxabicyclic moiety in **6a** in order to generate a seven-membered carbocyclic ring system. To this end, Lewis acid-mediated nucleophilic cleavage[6,7] was first considered. Treatment of **6a** (the major isomer) with excess triethylsilane (8 equiv.) in the presence of titanium tetrachloride ($TiCl_4$) (3 equiv.) in dichloromethane at −70°C afforded **9** as a single diastereoisomer in 90% yield after flash column chromatography. In the same manner, addition of allyltrimethylsilane to **6a** gave the tetracyclic compound **10** in 75% yield (Scheme 4). These structures were

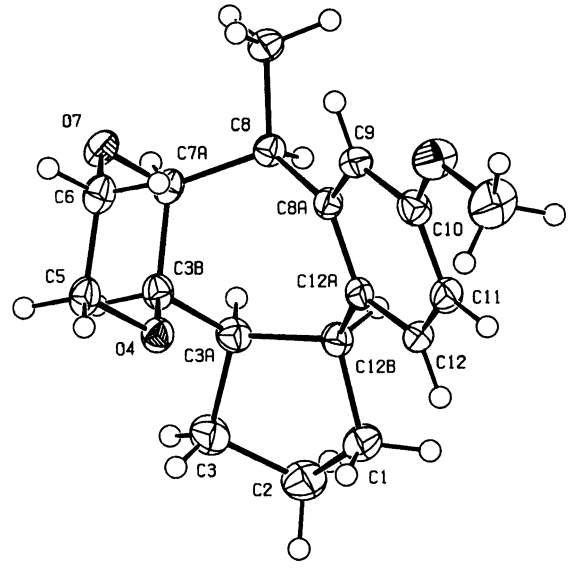
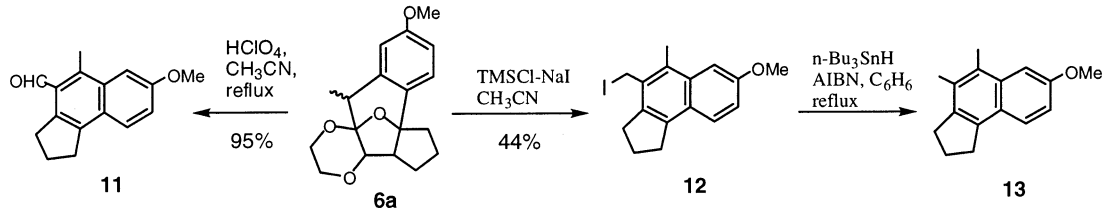
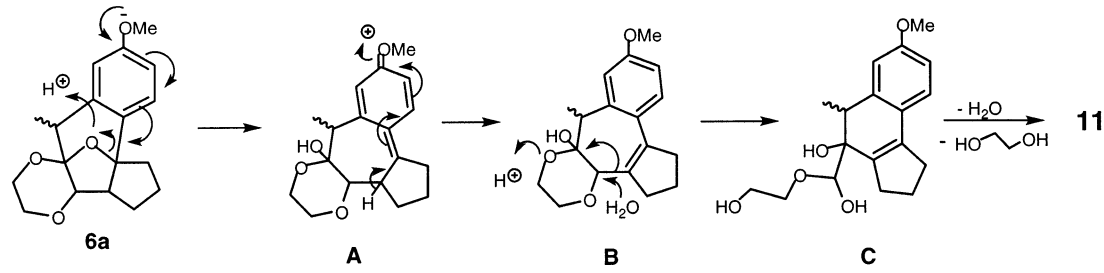


Figure 1. ORTEP drawing of **9**.



Scheme 5.



Scheme 6.

assigned on the basis of an extensive NMR study (COSY, NOESY and HETCOR spectra) and have been confirmed by X-ray crystallographic analysis (Fig. 1).[8] The formation of **9** and **10** is the overall result of sequential double addition of the nucleophile (hydride and allylsilane, respectively) from the same face, *syn* to each other.

In order to cleave the dioxene ring and release the oxygenated functionalities, acid hydrolysis of **6a** was undertaken. Treatment of ketal **6a** with perchloric acid in refluxing acetonitrile for three hours furnished the naphthalene derivative **11** in 95% after flash chromatography. This unexpected structure was established on the basis of ^{1}H, ^{13}C NMR, IR and mass spectra. A similar result was obtained when **6a** was submitted to iodotrimethylsilane. Treatment of **6a** with excess TMSI, in situ generated from chlorotrimethylsilane and sodium iodide in acetonitrile, led the iodomethylnaphthalene **12** in 44% yield. This structure was deduced from its spectroscopic data and confirmed by the following transformation: reduction of **12** with *n*-tributyltin hydride in the presence of a catalytic amount of AIBN in refluxing benzene for one hour gave the dimethylnaphthalene **13** (Scheme 5).

The formation of the naphthalene ring can be rationalized as illustrated in Scheme 6. Protonation of the furane ring occurs first and leads after cleavage of the ether bond to intermediate **B**. Acid-mediated opening of the dioxane moiety is followed by a pinacol-like rearrangement affording **C** which leads to **11** after hydrolysis of the hemiacetal and dehydration. Obviously, the driving force for this transformation is the formation of the highly stabilized aromatic system.

In summary, we have found that allylic alcohols **5**, readily prepared from 1,4-dioxene and methoxy-acetophenones, undergo acid-catalyzed triple-domino reactions leading to the pentacyclic acetal **6** which can be transformed into a fused seven-membered ring system or into naphthalene derivatives in high yields. Work to apply this reaction to the synthesis of natural products containing the 5,6,7-fused tricyclic systems is now under way.

References

1. For a review on domino reactions, see: Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115.
2. (a) Hanna, I.; Ricard, L. *Tetrahedron Lett*. **1999**, *40*, 863. (b) Hanna, I. *Tetrahedron Lett*. **1999**, *40*, 2521. (c) Hanna, I.; Michaut, V. *Org. Lett*. **2000**, *2*, 1141.
3. Fétizon, M.; Goulaouic, P.; Hanna, I.; Prangé, T. *J. Org. Chem*. **1988**, *53*, 5673.
4. Spectroscopic and analytical data for compound **6a** (major isomer): Colorless crystals, mp 100–101°C. IR ν_{max} 1610, 1579 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 1H, $J=8.4$ Hz), 6.74 (d, 1H, $J=2.2$ Hz), 6.67 (dd, 1H, $J=8.4$ and 2.2 Hz), 4.16 (td, 1H, $J=11.6$ and 2.8 Hz), 3.84 (d, 1H, $J=7.4$ Hz), 3.79 (s, 3H, OMe), 3.77 (d, 1H, $J=12.8$ Hz), 3.55–3.70 (m, 2H), 2.80 (q, 1H, $J=7.0$ Hz), 2.30–2.40 (m, 1H), 2.20–2.30 (m, 1H), 1.95–2.25 (m, 3H), 1.75–1.90 (m, 1H), 1.47–1.66 (m, 1H), 1.35 (d, 3H, $J=7.0$ Hz) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.4 (C), 141.4 (C), 134.0 (C), 120.9 (CH), 115.0 (CH), 110.8 (CH), 102.4 (C), 89.5 (C), 78.0 (CH), 63.3 (CH_2), 61.1 (CH_2), 57.6 (CH_3, OMe), 55.3 (CH), 42.3 (CH), 32.4 (CH_2), 27.2 (CH_2), 25.6 (CH_2), 18.8 (CH_3) ppm. MS (CI, NH_3), m/z 303 (M+1), 320 (M+18). Elemental analysis (%) calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.01; H, 7.33.
5. For a recent example involving intramolecular Friedel–Crafts alkylation in domino reactions see: Knölker, H.-J.; Baum, E.; Graf, R.; Jones, P. G.; Spieß, O. *Angew. Chem., Int. Ed* **1999**, *38*, 2583.
6. For a review on Lewis acid-mediated addition to acetals see: Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043–1054.

7. For recent examples on addition of nucleophiles to cyclic acetals, see: Fujiwara, K.; Amano, A.; Tokiwano, T.; Murai, A. *Tetrahedron* **2000**, *56*, 1065. Wu, H.-S.; Chern, J.-H. *J. Org. Chem.* **1997**, *62*, 3208. Pellissier, H.; Santelli, M. *J. Chem. Soc., Chem. Commun.* **1995**, 607.
8. Crystallographic data for compounds **9** and **10** have been deposited with the Cambridge Crystallographic Data Centre.