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Preliminary communication/Communication

Anti-Markovnikov stereoselective addition of bis(trimethylsilyl)octadiene to ketal obtained by unprecedented retro-Claisen condensation of 3-hydroxy-2,4-pentanedione bis-ketal

Addition stéréosélective et anti-Markovnikov du bis(trimethylsilyl)octadiène sur un cétal obtenu par une condensation inattendue de type rétro-Claisen du 3-hydroxy-2,4-pentanedione bis-cétal

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ABSTRACT

In the course of the Lewis acid-mediated cycloaddition of 1,8-bis(trimethylsilyl)-2,6-octadiene to bis-ketals, we have observed an unprecedented retro-Claisen condensation from the ketalisation of a 3-hydroxy-2,4-pentadione giving rise to a substituted 2,2,3-trimethoxybutane and an anti-Markovnikov stereoselective cycloaddition of the 1,8-bis(trimethylsilyl)-2,6-octadiene to this latter ketal.

Mots clés :
Allylsilane
Condensation de rétro-Claisen
Cétalisation
Addition anti-Markovnikoff
Réactions de cyclisation

RÉSUMÉ

Au cours de la cycloaddition catalysée par un acide de Lewis du 1,8-bis(triméthylsilyl)-2,6-octadiène sur un bis-cétal, nous avons observé une condensation inattendue de type rétro-Claisen au cours de la cétalisation de la 3-hydroxy-2,4-pentadione conduisant au 2,2,3-triméthoxybutane et une addition stéréosélective et anti-Markovnikoff du bis(triméthylsilyl)octadiène sur ce dernier cétal.

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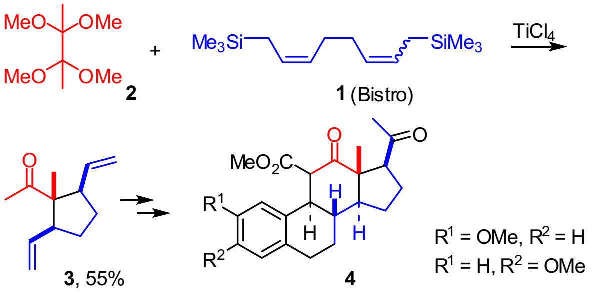
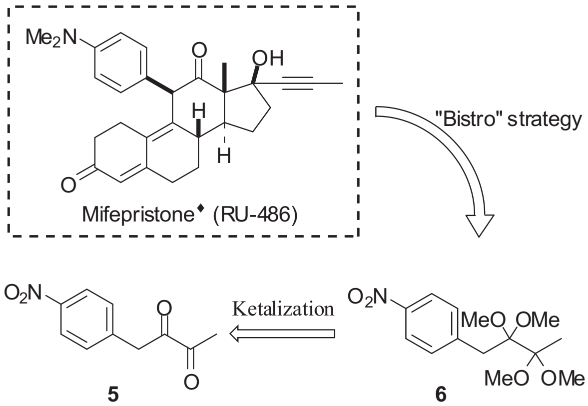
1. Introduction

The addition of the 1,8-bis(trimethylsilyl)-2,6-octadiene (Bistro) 1 to various ketals afforded a large variety of 1,1-disubstituted-2,5-divinylcyclopentanes.[1] Some of them proved to be valuable building blocks for the synthesis of unnatural steroids[2] or vitamin D derivatives [3]. Scheme 1 shows a good example of this strategy [4].

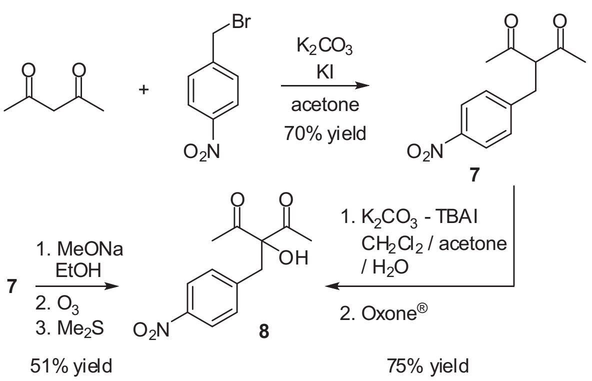
Then, we have intended to synthesize 11-dimethylaminophenyl steroids analogous of Mifepristone® (RU 486) [5], and other similar antiprogestative steroids [6]. For this



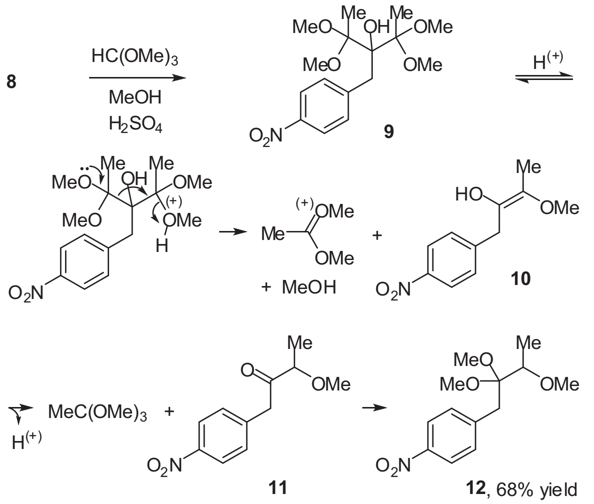
Scheme 1. (Color online) Synthesis of unnatural steroids from Bistro 1 and bis-ketal 2.



Scheme 2. Planned synthesis of α-bis-ketal 6.



Scheme 3. Synthesis of 3-hydroxy-3-(4-nitrobenzyl)pentane-2,4-dione 8 from acetylacetone.

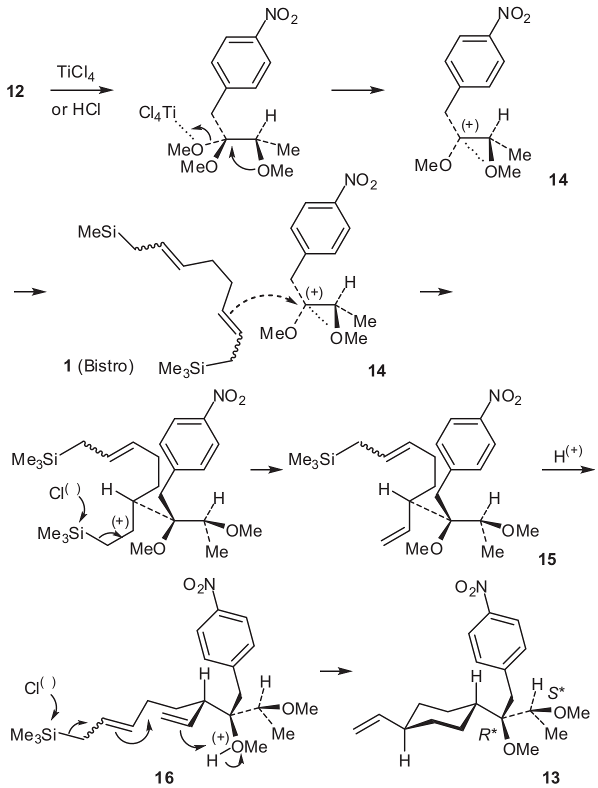


Scheme 4. Preparation of 1-(4-nitrophenyl)-2,2,3-trimethoxybutane 12 from 8.

purpose, it was necessary to synthesize the 1-(4-nitrophenyl)butane-2,3-dione diketal 6 from the 1-(4-nitrophenyl)butane-2,3-dione 5 (Scheme 2).

2. Synthesis of α-diketone 5

Only few methods are known to synthesize α-diketones [7]. Among them, we chose the ozonolysis



Scheme 5. Synthesis of diether 13 from 12 and Bistro 1.

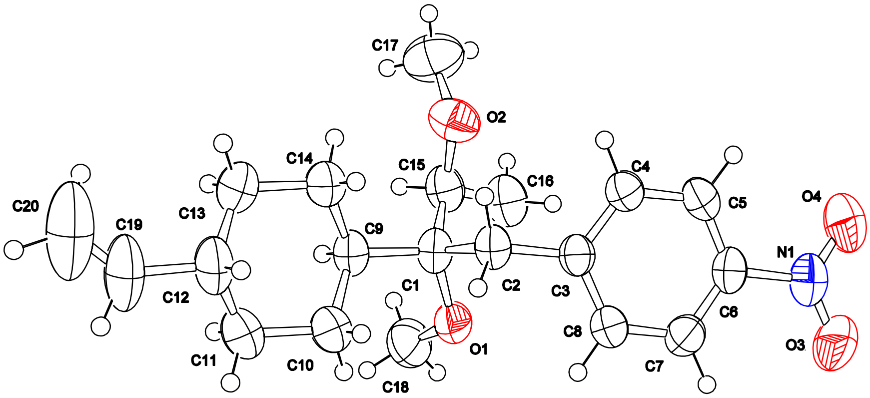


Fig. 1. (Color online) ORTEP diagram of compound 13 [22]. The atomic displacement parameters are drawn at the 50% probability level.

of the corresponding β-diketone enolates as it appears to be straightforward. In our case, the suitable 3-(4-nitrobenzyl)pentane-2,4-dione 7 was obtained by alkylation of acetylacetone with *p*-nitrobenzyl bromide [8] in 70% yield [9]. Surprisingly, ozonolysis of 7 in basic medium followed by the treatment with dimethylsulfide afforded 3-hydroxy-3-(4-nitrobenzyl)pentane-2,4-dione 8 in 51% yield and not the expected α-diketone 5 [10]. To confirm the structure of 8, we also prepared it by treatment of 7 by Oxone® in basic medium (75% yield) (Scheme 3) [11,12].

Ketalization of 8 with methanol in the presence of trimethyl orthoformate and a catalytic amount of sulfuric acid did not lead to the corresponding bis-ketal 9 but to the unexpected 1-(4-nitrophenyl)-2,2,3-trimethoxybutane 12 [13]. This compound resulted from a retro-Claisen like condensation [14,15] in acidic medium. Indeed, after formation of 9, its protonation allowed a fragmentation reaction [16] with formation of enol 10 and then ketalisation of the corresponding tautomeric α-methoxyketone 11 to give 12 (Scheme 4).

The retro-Claisen condensation is a well-known reaction in basic medium and the usual reagents are metal alkoxides and recently Lewis acid salts [17], but, to the best of our knowledge, it was never previously reported in protic medium.

3. Addition of bis(trimethylsilyl)octadiene (Bistro) to ketal 12

The addition of Bistro 1 to ketal 12 led stereoselectively to the unexpected product 13 (Scheme 5) [18]. The structure of 13 was established by spectral data, and then confirmed by a X-ray crystal structure determination (Fig. 1) which revealed two stereogenic centers with the relative configurations R^* and S^* and the presence of a trans-disubstituted cyclohexane.

The unexpected formation of 13 could be rationalized by the following mechanism. First, $TiCl_4$, or adventitious HCl, led to the stabilized methoxycarbenium ion 14, then, a stereoselective attack of one allylsilane moiety from 1 afforded 15. Then, a protonation of the methoxy group by adventitious HCl gave 16. Finally, a cascade reaction induced by the addition of a chloride anion to the second silicon atom and only the regioselective delivery of this proton to the internal carbon atom of the vinyl group (anti-Markovnikov addition) [19] can explain the stereoselective formation of 13 (Scheme 5). In 16, the protonated methoxy group induces a polarization of the vinyl group, thus increasing the electrophilic properties of the terminal methylene group and stimulating the anti-Markovnikov nucleophilic attack from the second allylsilane moiety.

Because of this proximal effect, the primary nascent carbocation may be promptly captured by the nucleophilic double bond of the second allylsilane moiety [20].

In previous works, we have reported that the addition of Bistro 1 to 2,4-pentanedione mono-ethylene ketal or 2-acetylcyclohexanone mono-ethylene ketal [1b], or 2-methyl-1,3-cyclohexanedione mono-catechol ketal [21], gave rise to bi- or tricyclic alcohols following a similar mechanism, but with a regular Markovnikov electrophilic addition of the carbonyl group to the vinyl group.

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[12] 3-Hydroxy-3-(4-nitrobenzyl)pentane-2,4-dione (8). Method A: Ozonolysis: A 500-mL three-neck flask equipped with a stirring bar, was charged with anhydrous ethanol (325 mL), sodium methylate (8.75 g, 162 mmol) and 3-(4-nitrobenzyl)pentane-2,4-dione 7 (CAS number: 56699-21-9) (19.1 g, 81.2 mmol). The stirred mixture was cooled to–60 °C and ozone in oxygen was bubbled through the stirred solution for 4 h. Then the mixture was flushed with argon and dimethylsulfide (11 mL, 0.15 mol) was added. After stirring at room temperature for 1 h, tartaric acid (20 g. 0.13 mol) was added and the suspension was stirred for 1 h, and then filtered and washed with CH_2Cl_2 and concentrated under *vacuo* to give red oil. The crude product was purified by flash-chromatography on silica gel (petroleum ether/diethyl ether, 70:30) to give alcohol 8 (10.4 g, 41.4 mmol, 51%). Method B: Enolate oxidation. To a solution of 7 (4.70 g, 20.0 mmol), K_2CO_3 (27.6 g, 0.20 mol), and tetrabutylammonium iodide (1.48 g, 4.0 mmol) in CH_2Cl_2, acetone, and water (1/1/1, 600 mL) stirred at 0 °C was added Oxone® (74 g, 0.12 mol) in water (600 mL) over 30 min. After stirring at 0 °C for 3 h, the mixture was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtrated, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 50:50) to give 8 (3.76 g, 15.0 mmol, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.07 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 1H), 3.32 (s, 2H), 2.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.1 (s)(2 C), 147.3 (s), 142.4 (s), 131.2 (d)(2 C), 123.4 (d)(2 C), 90.7 (s), 41.3 (t), 25.5 (q)(2 C). $C_{12}H_{13}NO_5$ (251.24): C 57.37, H 5.22; found C 57.42, H 5.28.

[13] 1-(4-Nitrophenyl)-2,2,3-trimethoxybutane (12). A 250-mL round-bottomed flask equipped with a stirring bar, was charged with anhydrous methanol (42 mL), trimethyl orthoformate (84 mL), 8 (4.40 g, 17.5 mmol) and conc. sulfuric acid (0.40 mL, 7.5 mmol). The mixture was stirred at reflux for 10 h. Then, a saturated aqueous solution of $NaHCO_3$ was added and after usual work-up, the mixture was concentrated under *vacuo* and the crude product was purified by flash chromatography on silica gel (petroleum ether-diethyl ether, 70:30) to give 12 (3.22 g, 12.0 mmol, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.07 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 3.32 (q, *J* = 6.5 Hz, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 3.24 (s, 3H), 3.14 (½AB, *J* = 14.2 Hz, 1H), 3.0 (½AB, *J* = 14.2 Hz, 1H), 1.0 (d, *J* = 6.5 Hz, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 146.6 (s), 145.7 (s), 131.7 (d)(2 C), 123.0 (d)(2 C), 103.1 (s), 78.6 (d), 57.2 (q), 49.6 (q), 49.3 (q), 38.0 (t), 14.5 (q). $C_{13}H_{19}NO_5$ (269.29): C 57.98, H 7.11; found C 58.12, H 7.18.

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[18] (2*R**,3*S**)-2,3-Dimethoxy-1-(4-nitrophenyl)-2-(trans-4-vinylcyclohexyl)butane (13). In a 100-mL two-neck flask equipped with a magnetic bar and an outlet of argon, was added anhydrous nitromethane (1.62 mL, 29.7 mmol) and anhydrous CH_2Cl_2 (34 mL). The solution was cooled to–70 °C and $TiCl_4$ (4.20 mL, 37.2 mmol) was added. Then 12 (2.00 g, 7.43 mmol) diluted in anhydrous CH_2Cl_2 (5 mL) was slowly added in 0.5 h. The solution was cooled to–90 °C and Bistro 1 (3.80 g, 14.9 mmol) diluted in anhydrous CH_2Cl_2 (5 mL) was added. The solution was stirred at–90 °C for 2 h and then overnights at–60 °C. Then, the solution was poured onto aqueous saturated NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed until neutrality and possibly filtrated on Celite®. The solution was dried over $MgSO_4$, and concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a gradient of petroleum ether-diethyl ether (100:0 to 50:50) to give 13 as a yellow solid (1.34 g, 3.86 mmol, 52%). ^{1}H NMR ($CDCl_3$, 300 MHz) 8.07 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 5.70 (ddd, *J* = 17.1, 10.4, 6.2 Hz, 1H), 4.91 (br. d, *J* = 17.1 Hz, 1H), 4.84 (br. d, *J* = 10.4 Hz, 1H), 3.40 (q, *J* = 6.4 Hz, 1H), 3.31 (s, 3H), 3.26 (s, 3H), 3.14 (½AB, *J* = 14.1 Hz, 1H), 2.88 (½AB, *J* = 14.1 Hz, 1H), 1.84–1.72 (m, 5H), 1.58-1.48 (m, 2H), 1.15-0.97 (m, 3H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2 (s), 146.3 (s), 144.3 (d), 131.9 (d) (2 C), 122.8 (d) (2 C), 112.0 (t), 82.3 (s), 80.8 (d), 56.4 (q), 51.1 (q), 44.6 (d), 42.0 (d), 36.0 (t), 33.2 (t), 33.1 (t), 27.9 (t), 27.7 (t), 13.9 (q). $C_{20}H_{29}NO_4$ (347.45): C 69.14, H 8.41; found C 69.08, H 8.38.

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