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A Short and Efficient Annelation Sequence for the Synthesis of Bicyclic Intermediates in the Total Synthesis of Strigol and its Analogues

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Summary. A new annelation sequence was developed for the bicyclic diones **2**, intermediates in the total synthesis of strigol (**1**) and its analogues. The first step of the sequence is the conjugate addition of nitro alcohols **4** to cyclopentenone **5**, followed by an alkylative cyclization step and dehydrogenation.

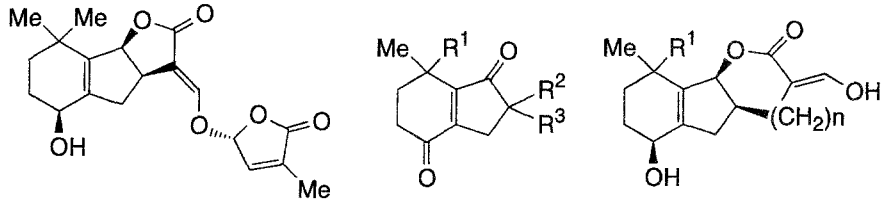
Keywords. Strigol; Nitroalkane annelation; *Michael* addition; *Nef* reaction; Bicyclic diones.

Eine kurze und effiziente Anellierungsmethode zur Synthese bicyclischer Zwischenprodukte in der Totalsynthese von Strigol und seinen Analogen

Zusammenfassung. Eine neue Anellierungsmethode zur Herstellung der bicyclischen Dione **2** (Zwischenprodukte in der Totalsynthese von Strigol (**1**) und seiner Analogen) wurde entwickelt. Der erste Schritt besteht in einer konjugierten Addition der Nitroalkohole **4** an die Cyclopentenone **5**. Anschließend erfolgen eine alkylierende Cyclisierung und eine Wasserstoffabspaltung.

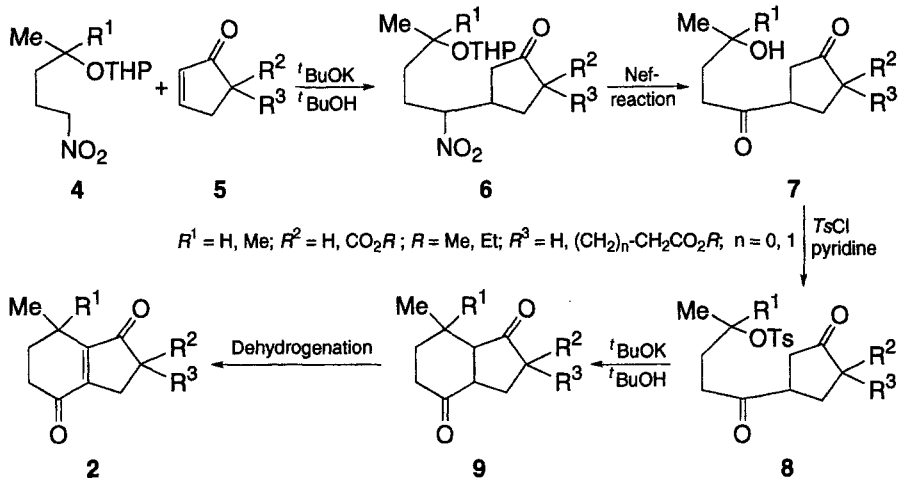
Introduction

During our synthetic work on the total synthesis of the potent germination stimulant strigol **1** and its analogs [1,2] we have developed a short and efficient annelation sequence for the synthesis of bicyclic diones **2**. These diones are suitable intermediates for the total synthesis of the tricyclic moiety **3** of strigol and various analogues (Scheme 1).



1 **2** **3**

Scheme 1

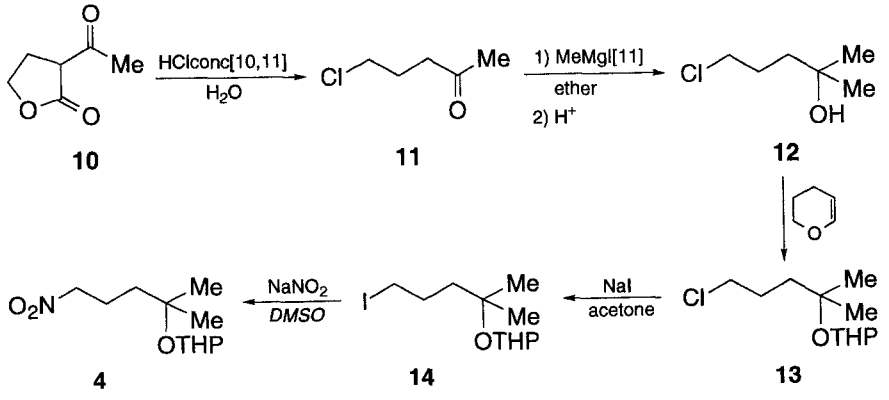


Scheme 2

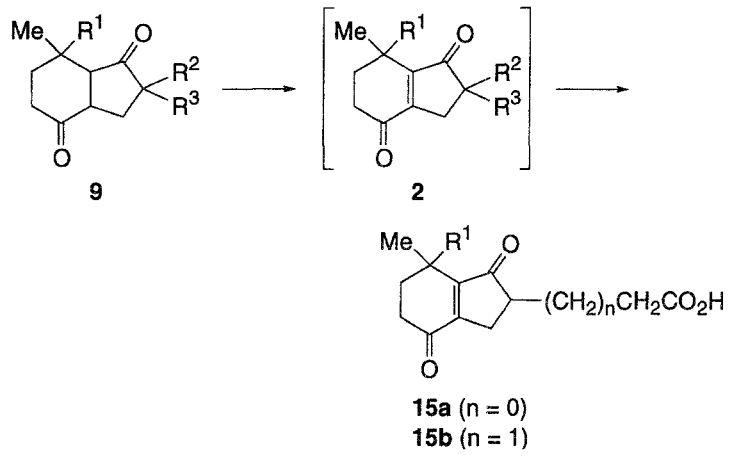
Results and Discussion

Our annellation sequence is based on the application of γ-nitro alcohols (**4**) which can be used effectively in a synthetic scheme employing a protection-deprotection technique for the efficient synthesis of bicyclic intermediates **2**. The first step in this novel annellation sequence is the conjugate (*Michael*) addition of suitable nitroalkanes **4** to cyclopentenones **5** [3] (monitroed by TLC or GC) (Scheme 2). The key step in the synthesis is an alkylative ring closure that can be achieved after the conversion of the nitro group into a carbonyl group (*Nef* reaction), *O*-deprotection, and tosylation. The ring closure was carried out with KO^{t}Bu. The annelation reaction, including the dehydrogenation after cyclization, is in fact a one-pot procedure.

The starting materials are commercially available products. Thus, **4** (R^1 = H) can be obtained from 3-buten-2-one with nitromethane [4, 5] followed by reduction with sodium borohydride [6, 7] and *O*-protection with dihydropyrane [8, 9]. The synthesis of another **4** (R^1 = Me) was achieved in a multistep synthesis from 2-acetyl-butyrolactone (**10**, Scheme 3).



Scheme 3



Scheme 4

Table 1. Experimental data of the one-pot annellation reactions

Compound **4**	Compound **5**		**Michael** addition		Overall yield
R^1	R^2	R^3	Reaction time (h)	Yield of **6** (%)	of isolated **9** or **15** (%)[b]
H	H	H	6	75	24
H	CO_2Me	CH_2CO_2Et	8	63	15
H	CO_2Me	$(CH_2)_2Et$	8	65	17
Me	CO_2Me	CH_2CO_2Et	16	45	9

[a] After column chromatography; [b] overall yield of five steps combined

The 2-cyclopentenone **5a** ($R^2 = R^3 = H$) is a commercially available compound. The corresponding diesters ($R^2 = CO_2R$; $R^3 = (CH_2)_nCH_2CO_2R$; $R = Me$, Et; $n = 0, 1$) were synthesized by a method reported earlier [3]. The *Nef*-reaction of adducts **6** was achieved by the reductive method of McMurray [13] with a buffered solution of $TiCl_3$. The tetrahydropyranyl protecting group of **6** was also hydrolyzed during the *Nef*-reaction. Careful tosylation of the corresponding hydroxy diones **7** furnished the alkylating tosylates **8**. The latter were cyclized with ^{t}BuOK in ^{t}BuOH to **9** without isolation. The diones **9** thus obtained were dehydrogenated to enediones **2** in an oxygen atmosphere. The diesters **2** were then hydrolyzed and decarboxylated in acidic medium to give acids **15** (Scheme 4, Table 1).

Hydrindaneacetic acid (**15a**, $n = 0$) and the corresponding propionic acid (**15b**, $n = 1$) were identical with the corresponding compounds obtained in our earlier syntheses [14, 15]. These acids can be used in the total synthesis of strigol and its analogues.

Experimental

Melting points (uncorrected) were determined on either a Büchi 510 or a Gallenkamp automatic MP apparatus or in open capillary tubes. Infrared spectra were recorded on a Nicolet FT-IR or a Perkin-Elmer 1600 Series FT-IR apparatus. ^1H and ^{13}C NMR spectra were obtained on either of the following NMR spectrometers: Perkin-Elmer R12 (^1H: 60 MHz), Bruker AW 80 (^1H: 80 MHz), Jeol FX 100 (^1H: 100 MHz), Varian unity 300 (^1H: 300 MHz), Bruker AC 250 (^1H: 250 MHz) AC 400 (^1H: 400 MHz), and AM 500 (^1H: 500 MHz); chemical shifts δ (ppm relative to *TMS*). Merck Kieselgel 60 was used for TLC and column chromatography. Elemental analyses were performed on automated analyzers by the Richter Gedeon Chemical Co. RT or the EGIS Pharmaceutical Co. RT (Budapest, Hungary) and are in accordance with the calculated values.

5-Nitro-pentane-2-ol [6, 7]

Colorless oil; yield 64%; b.p.: 72–76 °C/0.3 mmHg (Ref. [6]: 101–102.5 °C/2 mmHg); $n_D^{24} = 1.4458$ (Ref. [7]: $n_D^{20} = 1.4494$).

2-(2'-Tetrahydropyranyloxy)-5-nitro-pentane (**4a**; $R^1 = H$)

20.0 g (0.15 mol) distilled 5-nitropentane-2-ol was dissolved in 300 ml of methylene chloride. To this solution, 21.0 g (0.25 mol, 22.8 ml) dihydropyrane and pyridinium tosylate [8, 9] (2.5 g, 0.01 mol) were added, and the reaction mixture was stirred for 6 h at room temperature. After the reaction, the solution was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous $MgSO_4$, and evaporated in vacuum. The yellowish oily residue was distilled in vacuum to give the title compound **4a** (22.2 g, 68%) as a colorless liquid. B.p.: 85–90 °C/0.3 mmHg; IR (film): 1555, 1380 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.06 and 1.18 (3H, doublets, $J = 6.2$ Hz, CH_3–CH–), 1.43–1.72 (m, 8H), 1.94–2.13 (m, 2H, CH_2–CH_2–NO_2), 3.35–3.48 (m, 1H, CH_3–CH–O), 3.65–3.85 (m, 2H, CH_2–O), 4.33–4.42 (m, 2H, CH_2NO_2), 4.52–4.63 (m, 1H, O–CH–O).

5-Chloro-2-methyl-2-pentanol (**12**)

Freshly distilled 5-chloro-2-pentanone [10, 11] (24.1 g, 0.2 mol) was dissolved in anhydrous ether. To this stirred and colled solution, 400 ml ethereal solution of MeMgI (prepared from 28.4 g (0.2 mol) of MeI and 4.4 g (0.18 g atom) Mg) was added at a rate that allowed to keep the temperature of the reaction mixture below 10 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 1 h. A mixture of diethyl ether (100 ml) and glacial acetic acid (50 ml) was added to the stirred reaction mixture, followed by 500 ml of water. The organic layer was separated. The aqueous layer was then extracted with three 250 ml portions of ether. The combined ethereal layers were washed with a saturated sodium bicarbonate solution (twice, 350 ml portions) and brine, dried over anhydrous $MgSO_4$, and evaporated. The yellow, oily residue was purified by distillation to give the title product **12** (17.6 g, 0.13 mol, 64%) as an almost colorless liquid. B.p.: 52–55 °C/0.7 mmHg (Ref. [11]: b.p.: 80–83 °C/16 mmHg); $n_D^{24} = 1.4493$ (Ref. [11]: $n_D^{20} = 1.4522$); IR (film): 3380, 1125 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$, δ, ppm): 1.24 (s, 6 H, Me_2C–O–), 3.55 (t, 2 H, Cl–CH_2–), 1.38–2.15 (m, 4 H, –CH_2–CH_2–CH_2–Cl).

2-Methyl-2-(2'-tetrahydropyranyloxy)-5-chloro-pentane (**13**)

5-Chloro-2-methyl-2-pentanol (**12**; 13.6 g, 0.1 mol) was dissolved in diethyl ether (125 ml). This solution was treated with dihydropyrane (15.1 g, 0.18 mol, 16.4 ml) and *p*-toluenesulfonic acid (0.1 g) and stirred for 3 h. At the beginning of the reaction the solvent started to boil spontaneously but later cooled down to room temperature. The reaction mixture was filtered through a layer of alumina (100 g, grade I,

neutral) in a short column and the solvent was removed in vacuum. The residue was purified by distillation in vacuum to give a colorless liquid (13.9 g, 63%). B.p.: 98–102 °C/0.5 mmHg (Ref. [12]: b.p.: 120–130 °C/12 mmHg); $n_D^{24} = 1.4589$ (Ref. [12]: $n_D^{20} = 1.4600$–1.4610); ^{1}H NMR (60 MHz, $CDCl_3$, δ, ppm): 1.23 (s, 6H, Me_2–C–O–), 1.25–2.1 (m, 10H), 3.43 (t, 2H, $J = 6$ Hz, Cl–CH_2–), 3.52 (m, 1H, Me_2–C*H*–O–), 3.87 (m, 2H, –CH_2–O–), 4.75 (m, 1H, –O–CH–O–).

2-Methyl-2-(2′-tetrahydropyranyloxy)-5-iodo-pentane (**14**)

2-methyl-2-(2′-tetrahydropyranyloxy)-5-chloro-pentane (**13**; 11.0 g, 50 mmol) was dissolved in anhydrous acetone (30 ml). This solution was stirred and treated with a solution of sodium iodide (9.0 g, 60 mmol) in anhydrous acetone (60 ml). After the addition, the reaction mixture was stirred for further 18 h, diluted with 200 ml of water, and extracted with hexane (five times, 150 ml portion of hexane each). The combined organic layers were dried over $MgSO_4$, filtered through a short Kieselgel column, and evaporated in vacuum. The remaining organe oil (9.2 g, 59%) was used without further purification in the next step. An analytical sample was further purified on a Kieselgel column with hexane:ethyl acetate = 8:1. IR (film): 2950, 2875, 1150, 1075, 1020, 975 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$, δ, ppm): 1.25 (s, 6H, Me_2–C–O–), 1.20–2.25 (m, 10H), 3.27 (t, 2H, I–CH_2–), 3.50 (m, 1H, Me_2–C*H*–O–), 390 (m, 2H, –CH_2–O–), 4.65 (m, 1H, –O–CH–O–).

2-Methyl-2-(2′-tetrahydropyranyloxy)-5-nitro-pentane (**4**, R^1 = Me)

2-Methyl-2-(2′-tetrahydropyranyloxy)-5-iodo-pentane (**14**; 7.8 g, 25 mmol) was dissolved in anhydrous *DMSO* (25 ml). To this stirred solution, powdered and dried $NaNO_2$ (2.1 g, 30 mmol) in anhydrous *DMSO* (40 ml) was added carefully. The reaction mixture warmed up and a solid (NaI) separated which was removed by filtration after the reaction mixture had cooled to room temperature. The remaining solution was poured onto 200 ml of water and extracted with hexane (five portions, 75 ml each). The combined organic layers were then dried over anhydrous $MgSO_4$ and evaporated in vacuum. The remaining oil was then purified by distillation using a short-path distillation apparatus to give a pale yellow liquid (24 g, 41%). B.p.: 79–83 °C/0.1 mmHg; IR (film): 1555, 1380 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.28 (s, 6H, Me_2–C–O–), 1.27–1.85 (m, 8H), 1.90–2.12 (m, 2H, –C*H*$_2$–CH_2–NO_2), 3.40–3.52 (m, 1H, CH–O–), 3.62–3.87 (m, 2H, CH_2–O–), 4.35–4.45 (m, 2H, –CH_2–NO_2), 4.55–4.65 (m, 1H, –O–CH–O–).

General procedure for the annelation of nitro compounds **4** *with cyclopentenones* **5** *(according to* Scheme 2 *and* Table 1*) to give enediones* **2**

The selected nitro compound **4** (15 mmol) and a given cyclopentenone **5** (15 mmol) were dissolved in anhydrous *tert*-butanol. This solution was treated with a solution of ^{t}BuOK (0.17 g, 1.5 mmol) in anhydrous ^{t}BuOH (10 ml). The reaction mixture was then stirred (Table 1) under nitrogen, and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and diluted with diethyl ether (80 ml), washed with a 0.1 *M* solution of HCl followed by brine, dried over anhydrous $MgSO_4$, and evaporated. The orange oil thus obtained was purified on a Kieselgel column with hexane:ethyl acetate = 7:3. The almost colorless viscous oil or pale yellow semisolid **6** (depending on the substituents) thus obtained was dissolved in *THF* (20 ml) and treated with sodium methylate in methanol (0.35 g (0.15 g atom) Na metal dissolved in 20 ml of methanol) at 10 °C. A buffered solution of $TiCl_3$ (23.5 g of ammonium acetate was dissolved in 70 ml of water and mixed with 70 ml of 15% w/v $TiCl_3$ solution (about 0.1 mol) was then added into the vigorously stirred reaction mixture under nitrogen. After 1 h the reaction mixture was extracted with diethyl ether (five times, 50 ml portion each). The combined etheral layers were then washed with a solution of $NaHCO_3$ until neutral, dried over anhydrous $MgSO_4$, and evaporated in vacuum. The remaining pale yellow oil **7** showed one spot on TLC and was transformed further without purification.

The oily **7** was dissolved in a mixture of *THF* (20 ml) and anhydrous pyridine (10 ml) and treated dropwise with freshly distilled *p*-toluenesulfonic acid chloride (2.28 g, 12 mmol) over 30 min. The reaction mixture was stirred for further 3.5 h and then diluted with 150 ml of ether. The etheral solution was washed three times with an 1 *M* HCl (50 ml portions), followed by three washings with a saturated sodium bicarbonate solution (25 ml portions). After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuum. The product **8** (a viscous oil) showed one spot on TLC. It was dissolved without further purification in a mixture of 15 ml of benzene and 15 ml of *tert*-butanol. This solution was treated under nitrogen with a solution of ^{t}BuOK (1.68 g, 12 mmol) in 15 ml of anhydrous ^{t}BuOH under stirring at room temperature for 30 min. The tosylate **8** was consumed during further stirring at room temperature for 2 h (TLC). Then, the reaction mixture was diluted with diethyl ether (75 ml), the etheral solution was washed with three 20 ml portion of 1 *M* HCl, followed by three washings with 20 ml portions of saturated $NaHCO_3$ solution. After drying over anhydrous $MgSO_4$ the solvent was evaporated in vacuum. The crude cyclized product **9** was a dark, viscous oil but showed only one spot on TLC. Chromatography on a Kieselgel column with hexane:ethyl acetate = 7:3 resulted in a colorless oil. This oil was then dissolved in a mixture of glacial acetic acid (10 ml) and 6 *M* HCl (10 ml) and boiled for 5 h under an oxygen atmosphere. The reaction mixture was then diluted with water (10 ml) and extracted four times with 25 ml portions of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated in vacuum. The semi-solid **2** was purified by column chromatography with a benzene:ethyl acetate:methanol = 8:2:1 eluent mixture.

2,3,4,5,6,7-Hexahydro-7-methyl-indene-1,4-dione (**2a**, $R^1 = R^2 = R^3 = H$)

The product was distilled in vacuum on a short-path distillation apparatus to give a colorless oil (0.59 g, 24% overall yield from **4a**, $R^1 = H$); b.p.: 90–92 °C/0.6 mmHg (Ref. [16]: b.p.: 110–130 °C/4 mmHg). Spectroscopic data are identical with those of material synthesized earlier by *Tobias* [16] and *Kádas* [17].

2,3,4,5,6,7-Hexahydro-2-carboxymethyl-7-methyl-indene-1,4-dione (**15a**; $R^1 = H$, n = 0)

The product crystallized from cold ether to give colorless crystals (0.5 g, 15% overall yield from **4a**); m.p.: 140–141 °C (Ref. [14]: m.p.: 141–142 °C). Spectroscopic data are identical with those of material synthesized earlier by *Kádas* [14].

2,3,4,5,6,7-Hexahydro-2-(2'-carboxyethyl)-7-methyl-indene-1,4-dione (**15b**; $R^1 = H$, n = 1)

The product crystallized to give a mass of semisolid, almost colorless crystals (0.6 g, 17% overall yield from **4a**). Spectroscopic data are identical with those of material synthesized earlier by *Kádas* [14].

2,3,4,5,6,7-Hexahydro-2-carboxymethyl-7,7-dimethyl-indene-1,4-dione (**15c**, $R^1 = Me$, n = 0)

The product crystallized from cold ether to give a mass of colorless crystals (0.28 g, 9% overall yield from **4b**); m.p.: 133–134 °C (Ref. m.p. [18]: 136–138 °C; Ref. [14]: m.p.: 133.5–134 °C). Spectroscopic data are identical with those of material synthesized earlier by *Raphael* [18] and *Kádas* [14].

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