Accepted Manuscript

Alternative synthetic approaches to *rac*-progesterone by way of the classic Johnson cationic polycyclization strategy

Rimantas Slegeris, Gregory B. Dudley

PII: S0040-4020(16)30173-9

DOI: 10.1016/j.tet.2016.03.041

Reference: TET 27581

To appear in: *Tetrahedron*

Received Date: 1 January 2016

Revised Date: 6 March 2016

Accepted Date: 11 March 2016

Please cite this article as: Slegeris R, Dudley GB, Alternative synthetic approaches to *rac*-progesterone by way of the classic Johnson cationic polycyclization strategy, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.03.041.

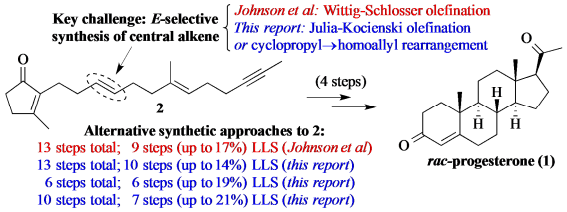
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Alternative synthetic approaches to *rac*-progesterone by way of the classic Johnson cationic polycyclization strategy

Leave this area blank for abstract info.

Rimantas Slegeris and Gregory B. Dudley*
Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390, USA



Tetrahedron
journal homepage: www.elsevier.com

Alternative synthetic approaches to *rac*-progesterone by way of the classic Johnson cationic polycyclization strategy

Rimantas Slegeris[a] and Gregory B. Dudley[a,]*

[a] *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390, USA*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
progesterone
total synthesis
traumatic brain injury (TBI)
process improvement
alkene synthesis

ABSTRACT

Three alternative synthetic entries into Johnson's classic synthesis of *rac*-progesterone are presented in this manuscript. *ent*-Progesterone, the non-natural enantiomer of progesterone, has recently been identified as a potential alternative to progesterone for investigations into possible prevention and treatment of traumatic brain injury (TBI). Difficulties in accessing *ent*-progesterone in large quantities prevent it from being studied more thoroughly. Strategies for producing synthetic *rac*-progesterone are described and discussed herein.

* Corresponding author. Tel.: +1-850-644-2333; fax: +1-850-644-8281; e-mail: gdudley@chem.fsu.edu

1. Introduction

Progesterone (**1**) is an abundant natural hormone that has a primary function of regulating the reproductive cycle in humans and other species. Progesterone has recently been reported also to reduce the negative effects associated with traumatic brain injury (TBI) *in vitro*.[1,2,3,4] Interactions between progesterone and transmembrane cell receptors in damaged mice brains can reduce swelling and inflammation,[5,6] although recent clinical studies failed to produce the corresponding positive outcomes in humans.[7] This discrepancy between rodent and human pharmacology will have to be resolved before progesterone can move forward as a potential therapeutic for TBI. Any potential utility of progesterone therapy, however, would also have to be balanced against the expected sexual side effects associated with administration of a reproductive hormone. These are two significant barriers to realizing the full therapeutic potential of progesterone for TBI.

An intriguing proposition for overcoming both pharmacological barriers is to explore the therapeutic potential of *ent*-progesterone, which displays superior activity to that of natural progesterone *in vitro*[8,9] against TBI. One can rationalize this unusual result by considering that both enantiomers of progesterone present peripheral carbonyl functionality bridged by a rigid hydrocarbon spacer (Figure 1). This topographical similarity seems to be sufficient for the molecular recognition events associated with TBI but not for reproductive cycle modulation. Therefore, there is reason to be optimistic that *ent*-progesterone can duplicate or enhance the TBI potential without the same degree of concern for sexual side effects.

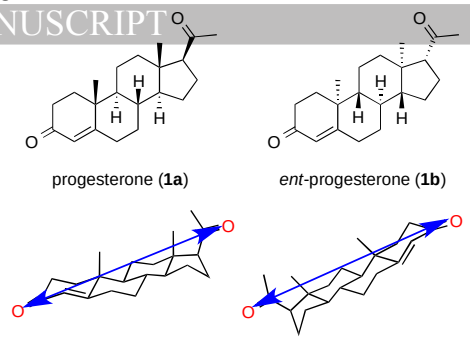
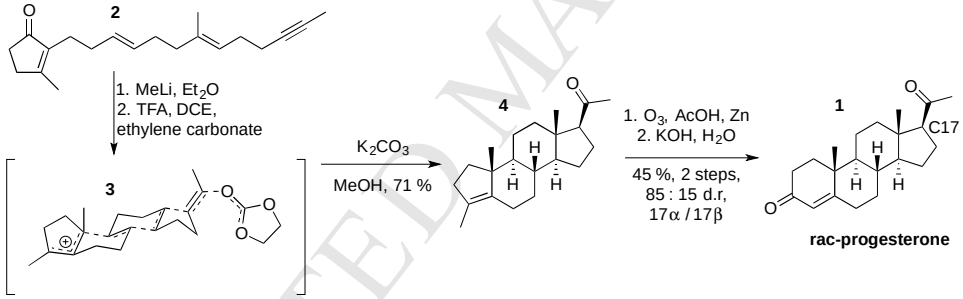
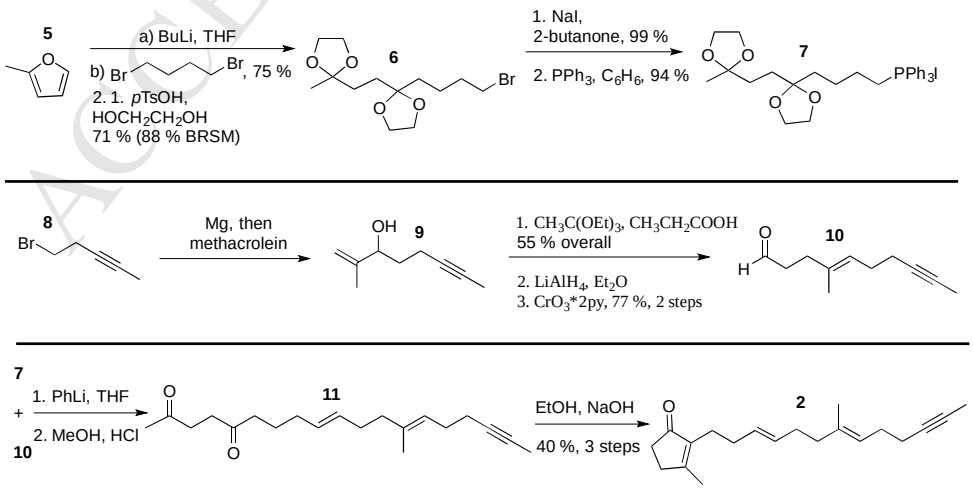


Figure 1. Skeletal stuctures and conformational drawings, showing the relative distance between the terminal oxygen atoms bridged by a hydrocarbon spacer, for natural progesterone (*left*) and *ent*-progesterone (*right*).

However, difficulties in accessing *ent*-progesterone prevent it from being studied more thoroughly as a potential drug candidate. *ent*-Steroids are only available through total chemical synthesis. Current access to *ent*-progesterone can be secured by leveraging an asymmetric synthesis of *ent*-testosterone,[10,11,12] or by resolution of *rac*-progesterone[13,14] by chiral preparative HPLC.[15] We decided to investigate alternative entries into the classic synthesis of *rac*-progesterone and aim to reduce the number of synthetic steps and increase the overall efficiency of the synthesis.



Scheme 1. Final steps in the classic Johnson synthesis of *rac*-progesterone. Trienyne **2** is converted into tetracycle **4** via key cation-π cyclization, which is followed by ozonolysis and aldol condensation to give *rac*-progesterone (**1**).



Scheme 2. Johnson's synthesis of trienyne **2**. *top*: Preparation of the olefination reagent. *middle*: Synthesis of aldehyde **10** by Johnson *ortho*-ester Claisen rearrangement. *bottom*: *E*-Selective Wittig–Schlosser olefination, followed by deprotection and aldol condensation to produce trienyne **2**.

Johnson's bio-inspired synthesis of *rac*-progesterone[13,14] is widely recognized as a landmark achievement in total synthesis.[16] Most significantly, it features a key cationic π-cyclization process, which is still a most attractive strategy for preparing synthetic progesterone (Scheme 1). Toward the end goal of making *ent*-progesterone more available, we endeavored to develop alternative processes for the synthesis of trienyne **2**, the substrate for Johnson's key cation-π cyclization event.

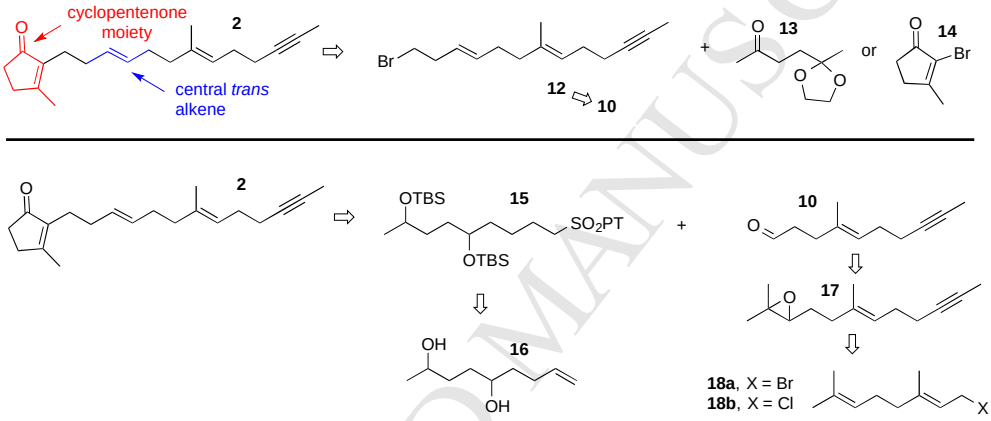
Johnson originally prepared trienyne **2** in 13 steps total, with a longest linear sequence of 9 steps,[17] for which we calculated an overall yield of up to 17%[18] (Scheme 2). A pivotal step in the sequence is an *E*-selective Wittig–Schlosser olefination of aldehyde **10**. The stereoselective formation of this *trans*-alkene is one of the central challenges in the synthesis of trienyne **2**. We initially conceived of exploiting sulfone-mediated olefination technology (i.e., Julia–Kocienski and related reactions) to craft this alkene. As discussed herein, we ultimately expanded our investigations to develop three alternative approaches to trienyne **2**. We also converted trienyne **2** to *rac*-progesterone according to the four-step sequence pioneered by Johnson.

2. Results and Discussion

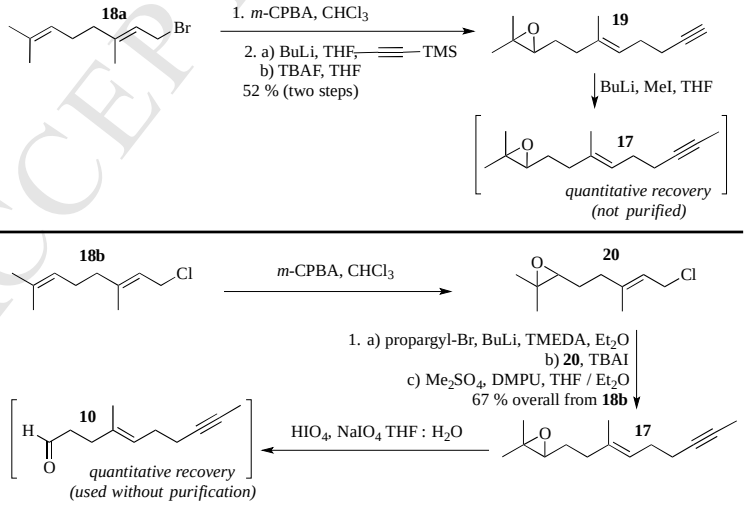
The synthesis of trienyne **2** was initially envisioned to involve parallel preparations of aldehyde **10** (cf. Scheme 2) and a pro-nucleophile partner exemplified by **15** (Scheme 3, bottom), which would be capable of delivering the cyclopentenone moiety and creating the central *trans*-alkene. We envisioned preparation of aldehyde **10** by the oxidative cleavage of epoxide **17**, which could be prepared from readily available geranyl halides (**18a**,**b**). We later investigated the conversion of homoallylic bromide **12** (Scheme 3, top) to the trienyne **2**, which proved advantageous.

2.1. Synthesis of aldehyde *10*

We started by devising an alternative route to known aldehyde **10**.[13,14,15,19] Epoxidation of geranyl bromide, followed by one-pot propargylation / deprotection[20] using lithiated TMS-propyne, gave terminal alkyne **19** in 52% yield over 2 steps (Scheme 4, top). Methylation followed by periodate cleavage of the epoxide then gave the desired aldehyde in 4 steps. However, this route is compromised by the relatively high cost of trimethylsilylpropyne and relative instability of the epoxidation product of geranyl bromide.



Scheme 3. Retrosyntheses of trienyne **2**. *top*: strategic disconnections involving homoallylic bromide **12** (prepared from aldehyde **10**) and either a pre-formed cyclopentenone (**14**) or a cyclopentenone precursor (**13**). *bottom*: first-generation approach featuring Julia–Kocienski olefination of aldehyde **10**, to be prepared from geranyl halides **18a** or **18b**.



Scheme 4. Alternative syntheses of aldehyde **10**, featuring epoxidation, homologation, and oxidative cleavage. *top*: Three-step homologation using lithiated TMS-propyne as a propyne dianion equivalent. *bottom*: One-pot homologation by double-lithiation of propargyl bromide, as outlined in Table 1.

Table 1. Optimization of the one-pot sequential double alkylation of dilithiopropyne ($C_3H_2Li_2$) depicted in Scheme 4

Entry	$C_3H_2Li_2$	Additive(s)	Methylating agent	Time and temperature[a]	Ratio **20:19:17**[b]	Yield %[c]
1	1.2 equiv	—	2.0 equiv MeI	Stage 1: –78 °C, 20 min Stage 2: –78 °C, 20 min	only **20**	N.D.
2	1.2 equiv	—	2.0 equiv MeI	Stage 1: 0 °C, 20 min Stage 2: 0 °C, 60 min	40:38:22	N.D.
3	1.2 equiv	—	3.0 equiv MeI	Stage 1: rt, 30 min Stage 2: 0 °C, 60 min	60:32:8	N.D.
4	1.5 equiv	10mol% TBAI	—	Stage 1: 0 °C, 30 min	32:68:—	N.D.
5	2.2 equiv	10mol% TBAI	—	Stage 1: 0 °C, 30 min	only **19**	81 (**19**)
6	2.2 equiv	10mol% TBAI 5.0 equiv DMPU	5.0 equiv MeI	Stage 1: 0 °C, 30 min Stage 2: rt, 60 min	7:33:60	N.D.
7	2.2 equiv	10mol% TBAI 5.0 equiv DMPU	5.0 equiv Me_2SO_4	Stage 1: 0 °C, 30 min Stage 2: rt, 60 min	only **17**	74 (**17**)
8[d]	2.2 equiv	10mol% TBAI 5.0 equiv DMPU	5.0 equiv Me_2SO_4	Stage 1: 0 °C, 30 min Stage 2: rt, 60 min	only **17**	76 (**17**)
9[d,e,f]	2.2 equiv	10mol% TBAI 5.0 equiv DMPU	5.0 equiv Me_2SO_4	Stage 1: 0 °C, 30 min Stage 2: rt, 60 min	complex and variable mixture	≤73 (**17**)
10[d,e,g]	2.4 equiv	10mol% TBAI 6.0 equiv DMPU	6.0 equiv Me_2SO_4	Stage 1: 0 °C, 30 min Stage 2: rt, 60 min	only **17**	67 (**17**)

[a]Stage 1: reaction of $C_3H_2Li_2$ with **12**; Stage 2: addition of methylating agent to the reaction mixture
[b]Estimated by ^{1}H NMR analysis of the crude product mixture.
[c]Isolated yield of the major product.
[d]Reaction mixture was quenched with 5% NH_3(aq) solution.
[e]8.33-mmol scale
[f]Stirring was compromised by formation of an insoluble sludge.
[g]THF was added as a co-solvent prior to Stage 2.

We therefore refined our approach and switched to geranyl chloride as a starting material. Both the epoxidation (with mCPBA) and the epoxide cleavage (with HIO_4) produced the expected products in the theoretically expected yields. The homologation of the allylic chloride to install the methylated alkyne (**20** → **17**) received the bulk of our attention.

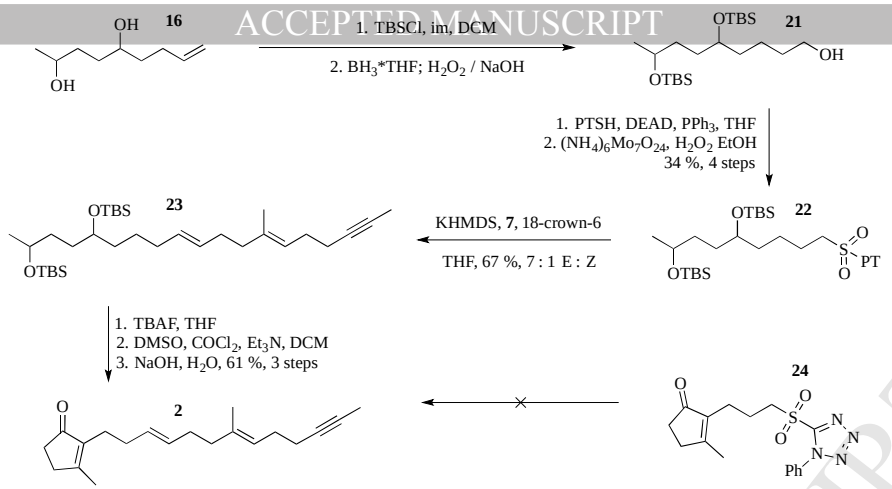
TMS-propyne (cf. Scheme 4, top) was in effect being employed here as a propyne dianion equivalent. Formally identifying lithiated TMS-propyne as a propyne dianion synthon inspired us to consider other possible options. Propargyl bromide (cf. Scheme 4, bottom) has been used to generate a propyne dianion suitable for one-pot sequential addition to a pair of aldehydes.[21] If this sequential addition strategy could be extended to sp^3-hybridized electrophiles (i.e., sequential substitution), then we could streamline this homologation process. Propargyl bromide is also cheaper than TMS-propyne.

We optimized for one-pot sequential *alkylation* of the $C_3H_2Li_2$ synthon as outlined in Table 1. During optimization, it was found that 2.2 equivalents of the propyne dianion (generated from propargyl bromide using *n*-butyllithium) and TBAI as an additive were necessary for complete conversion in the first stage of alkylation (entry 5). When methyl iodide was used as an alkylating agent, the second stage of the reaction was sluggish, giving mixtures of terminal and methylated alkyne. However, when 5 equivalents of dimethyl sulfate with DMPU as an additive was used, the reaction proceeded efficiently to completion on the exploratory scale (entry 8). Problems of solubility arose on larger scales (e.g., 8.33 mmol), with the formation of solid sludge on the bottom of the flask that complicated stirring and resulted in significantly decreased yields of the desired product (**17**). To avoid the insoluble sludge, the reaction was diluted with dry THF after the first stage, and the reaction time was extended to ensure completion. The epoxide of **17** was then cleaved with periodic acid / sodium periodate to give the desired aldehyde (**10**). In this manner, we were able to complete a concise and efficient synthesis of Johnson's aldehyde (**10**) in 3 steps and 67% overall yield from geranyl chloride (Scheme 4).

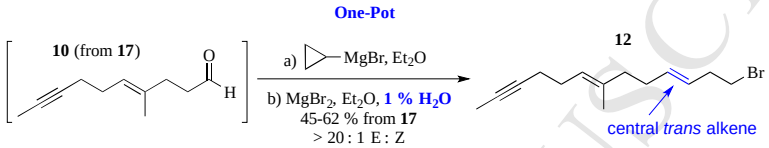
We then turned our attention to identifying and preparing appropriate coupling partners for homologating aldehyde **10** into the key cyclization substrate, **2**.

*2.2. Julia–Kocienski approach to trienynone **2***

We investigated the possibility of preparing **2** via Julia-Kocienski olefination (Scheme 5) as an alternative to the Schlosser–Wittig protocol previously employed by Johnson for installing the central *trans*-alkene. First, sulfone **22** was prepared in 4 steps from known diol **16**.[22] The diol was protected using TBSCl / imidazole in DMF. Hydroboration followed by Mitsunobu reaction and oxidation of the resulting sulfide using hydrogen peroxide / ammonium molybdate afforded **22** in 34% overall yield. *E*-selective Julia-Kocienski olefination[23] with aldehyde **10** then provided the desired olefination product in 67% yield and 7 : 1 *E* : *Z* ratio (as estimated by ^{1}H NMR). From here, intermediate **23** was converted to the desired **2** in 3 steps — TBS deprotection with TBAF, Swern oxidation of the resulting diol, and aldol condensation (61% yield over 3 steps). Attempts to make this route more convergent — namely, to olefinate the aldehyde using sulfone **24** — were unsuccessful, however, and the route from **16** was deemed too long (too many steps) for our prescribed objectives. Therefore, we abandoned the Julia-Kocienski strategy in favor of efforts to prepare the central *trans*-alkene by a cyclopropyl-homoallyl rearrangement.[24,25,26]



Scheme 5. Synthesis of **2** via Julia-Kocienski route.



Scheme 6. Synthesis of homoallylic bromide **12** by one-pot Grignard addition and S_N1-type substitution with stereoselective cyclopropyl→homoallyl rearrangement.

*2.3. Approaches to trienynone **2** via homoallyl bromide **12***

Cyclopropyl carbinols can be converted into homoallyl bromides stereoselectively and in good yield.[25,26] Cyclopropyl carbinols, in turn, can be prepared by addition of cyclopropyl Grignard reagents to aldehydes. Consequently, the conversion of aldehyde to homoallyl halide can be achieved in a two-step process comprising Grignard addition and subsequent rearrangement. We aimed to develop a one-pot protocol.

Addition of cyclopropylmagnesium bromide solution in diethyl ether to aldehyde **10**, followed by the dilution with diethyl ether and addition of magnesium bromide and small amounts of water (0.5–1%), gave satisfactory results (Scheme 6). The small amount of water was optimal: byproducts were observed in TLC analysis of reactions conducted under anhydrous conditions, and the rearrangement became sluggish with increasing concentrations of water. Thus, Grignard addition was followed by dilution with ether and addition of magnesium bromide and water. Heating this mixture overnight resulted in the desired one-pot transformation in 45-62% yield and high *E* : *Z* ratio (no *Z* isomer observed by ^{1}H NMR).

A convergent means of converting homoallylic bromide **12** to the desired ketone (**2**) would be by coupling **12** with bromo-cyclopentenone **14** (Scheme 7). However, we were unable to develop a satisfactory and reproducible protocol. Our best efforts involved borylation of **12** via the corresponding Grignard reagent, followed by Suzuki coupling with **14**. This sequence provided **2** in up to 46% yield, but it was capricious.

A more robust protocol for completing the route to **2** makes use of the classic tactic of alkylation and decarboxylation of β-keto esters, followed by aldol condensation.[27,28,29,30] β-Keto ester **25** was prepared according to the procedure reported by Crabbe *et. al.*[31] and alkylated with **12**. Saponification followed by one-pot decarboxylation, deprotection, and aldol condensation then gave the desired intermediate **2**.

2.4. Completion of the synthesis

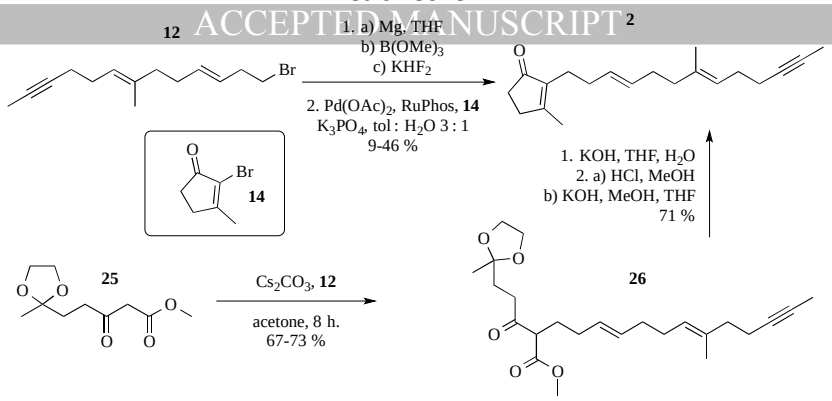
Having developed a new route to **2,** we then finished the synthesis of *rac*-progesterone using chemistry originally published by Johnson.[13] The overall efficiency of this 4-step transformation was similar to what was reported by Johnson; our yield for the MeLi addition and cation-π cascade sequence was slightly lower than originally reported, whereas our yield for the ozonolysis and aldol condensation sequence was slightly higher than originally reported.

3. Conclusion

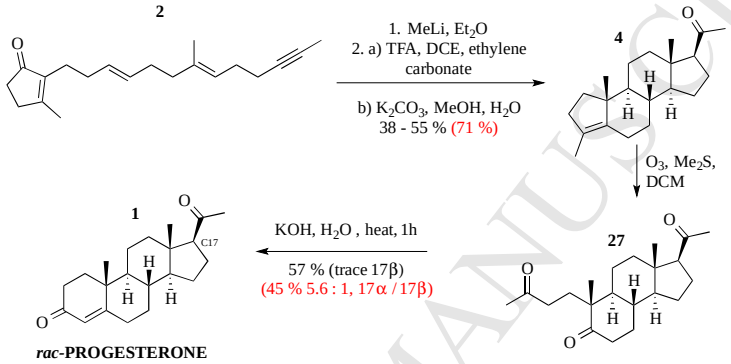
In conclusion, we report three alternative ways to access cation-π cyclization substrate **2** *en route* to *rac*-progesterone. These new methods may be viable for accessing larger amounts of *rac*-progesterone . During the course of our endeavors, we developed a straightforward process for converting a linear aliphatic aldehyde into a homoallylic bromide, which proved to be a good choice for preparing the isolated and unbranched central *trans*-alkene of **2** with high stereocontrol. The optimal route produces **2** in up to 21% overall yield for the seven-step longest linear sequence (LLS).

4. Experimental section

All reagents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded on a Bruker Ultrashield spectrometer operating at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR. The spectra were measured in $CDCl_3$ and are given as δ values (in ppm) relative to TMS. Column chromatography was carried out using compressed air, Silica Gel 60 (230– 400 mesh, Merck), and mixtures of ethyl acetate / hexanes. Mass spectra were recorded using electrospray ionization (ESI^+) or atmospheric pressure chemical ionization (APCI). All reactions were run under inert atmosphere unless otherwise indicated in the text. All solvents were purified using a Waters SG SiO_2 column based solvent purification system.



Scheme 7. Synthesis of trienynone **2** via Suzuki reaction and the alkylation route. The Suzuki coupling of **14** with boronates derived from **12** proved capricious and unreliable on small-scale, so we alternatively crafted the cyclopentenone moiety by aldol condensation after alkylation of β-keto ester **25** with bromide **12**.



Scheme 8. Completion of the synthesis of *rac*-progesterone (originally reported yields by Johnson in red in parentheses).

Yields refer to isolated yields of material judged to be ≥95% pure by ^{1}H NMR spectroscopy.

*4.1. (E)-4-methyldec-4-en-8-ynal (**10**)*

Geranyl chloride (5.8 g, 33.6 mmol, 1.0 equiv.) was dissolved in 336 mL of chloroform. Solution was then cooled to 0 °C and then *m*CPBA (77 % purity) (7.9 g, 35.3 mmol, 1.05 equiv.) was added in small portions over 30 min. After addition, solution was stirred for additional 30 minutes at 0 °C. Solution was then extracted 5 times with 1M $NaHCO_3$. Organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to give 6.34 g (100 % yield, ca. 90-95 % pure by ^{1}H NMR) of epoxide **20** as a colorless liquid, which was used in the next step without further purification and for which the characterization data matched literature values:[32] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.50 (td, 1H, J=7.9, 1.1), 4.10 (d, 2H. J=8.0), 2.69 (t, 1H, J=6.2), 2.29-2.11 (m, 2H), 1.74 (s, 3H), 1.66 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.7, 120.8, 63.8, 58.4, 40.8, 36.1, 26.9, 24.8, 18.7, 16.0. Propargyl bromide (2.97 g, 80 wt % in toluene, 20 mmol, 2.15 mL, 2.4 equiv.) was added dropwise to a cold (–78 °C) solution of BuLi (25 mL, 1.6 M in hexanes, 40 mmol, 4.8 equiv.) and TMEDA (1.162 g, 10 mmol, 1.5 mL, 1.2 equiv.) in 25 mL of ether. The resulting solution was stirred for 20 min at –78 °C, and then a mixture of epoxide **20** (1.572 g, 8.33 mmol, 1.0 equiv.) and TBAI (303 mg, 0.833 mmol, 0.1 equiv.) in 5 mL of ether was then added by cannula, followed by rinsing with two additional 5-mL portions of ether. The reaction mixture was then switched to a 0 °C bath and stirred for 1h, and then the cloudy mixture was diluted with 50 mL of THF and 6.41 g (50 mmol, 6.03 mL, 6.0 equiv) of DMPU, followed by the dropwise addition of 6.30 g (50 mmol, 4.78 mL, 6.0 equic.) of dimethyl sulfate. The 0 °C bath was then removed and the reaction stirred for 1 h at r.t. Reaction was then cooled to 0 °C and 25 mL of 5% NH_3 solution was added to quench the unreacted dimethyl sulfate. The reaction mixture was stirred for 1 h at r.t., then diluted with water, and extracted 3 times with ethyl acetate. Organic extracts were washed twice ammonium chloride, twice with water, and once with brine, and then dried over Na_2SO_4, concentrated under rotary evaporator and subjected to column chromatography using 3 % ethyl acetate / hexanes to afford 1.14 g (67 % yield) of **17** as a colorless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21 (t, 1H, J=5.6), 2.71 (t, 1H. J=6.3), 2.25-2.05 (m, 6H), 1.77 (t, 3H), 1.72-1.56 (m, 5H), 1.31 (s, 3H), 1.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.4, 123.6, 79.1, 75.4, 64.1, 58.4, 36.3, 27.7, 27.4, 24.9, 19.1, 18.7, 16.1, 3.5. **HRMS** (APCI) Calcd. for $C_{14}H_{23}O$ [M+H]: 207.1743, found: 207.1746. A cold (0 °C) solution of **17** (540 mg, 2.62 mmol, 1.0 equiv., prepared as described above) in 10.5 mL of 1 : 1 THF : H_2O was then treated with sodium periodate (1.35 g, 6.28 mmol, 2.4 equiv.), followed by the addition of periodic acid (59.7 mg, 0.262 mmol, 0.1 equiv.). The resulting mixture was stirred for 3 h at 0°C and 1 h at r.t. and then partitioned between cold (0 °C) 1 M $NaHCO_3$ and EtOAc. The aqueous layer was extracted with 3 portions of ethyl acetate. Organic layers were then combined and washed twice with water, brine and dried over sodium sulfate. Reaction mixture was then concentrated using rotary evaporator to give a quantitative recovery of crude aldehyde **10** (67% overall from geranyl chloride) as a colorless oil, which was used without purification in the next step. Characterization data for aldehyde **10** matched literature data:[14] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80-9.74 (t, 1H, *J*=1.2), 5.21 (t, 1H, *J*=5.7), 2.52 (tq, 2H, *J*=8, 1.2), 2.33 (t, 2H, *J*=8), 2.2-2.07 (m, 4H), 1.76 (t, 3H, *J*=2.4), 1.62 (s,

3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.6, 134.3, 124.1, 78.9, 75.6, 42.1, 31.8, 27.6, 19.0, 16.2, 3.4. Aldehyde **10** has strong irritating odor, which is felt even when the sample is in the fume hood.

*4.2. (6E,10E)-13-bromo-6-methyltrideca-6,10-dien-2-yne (**12**)*

Cyclopropylmagnesium bromide (7.82 mL, 0.5 M solution in Et_2O, 3.91 mmol, 1.5 equiv.) was added dropwise to a cold (0 °C) solution of aldehyde **10** (prepared as described above from 540 mg of epoxide **17**) in 10 mL of ether, and the resulting mixture was stirred for 30 min at 0 °C, then 30 min at r.t., and then recooled to 0 °C. Water (0.29 mL) was then added slowly. After an additional 5 min of stirring, the reaction mixture was diluted with 12 mL of Et_2O, and $MgBr_2$•Et_2O (3.35 g, 13.1 mmol, 5.0 equiv.) was added. The reaction mixture was then heated to reflux and stirred overnight. The reaction mixture was then cooled and partitioned between ethyl acetate and 1.0 M solution of $NaHCO_3$. The aqueous layer was extracted 2 times with EtOAc. Organic layer was then washed with $NaHCO_3$ (1.0 M), water, and brine, and dried over sodium sulfate and concentrated using rotary evaporator. The crude material was purified using column chromatography (gradient elution using hexanes to 1 % ethyl acetate / hexanes) to give 435 mg of homoallyl bromide **12** (62% yield from **17**, 42% over four steps from geranyl chloride) as a colorless oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.53 (dt, 1H, J=14.8, 8), 5.40 (dt, 1H. J=14.8, 8), 5.18 (t, 1H, J=5.2), 3.36 (t, 2H, J=8), 2.54 (q, 2H, J=8), 2.23-2.00 (m, 8H), 1.78 (t, 3H, J=2.8), 1.6 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.6, 133.4, 126.5, 123.3, 79.1, 75.4, 39.3, 36.0, 32.8, 30.9, 27.7, 19.2, 16.0, 3.45. **HRMS** (APCI) Calcd. for $C_{14}H_{20}Br$ [M–H]: 269.0722, found: 269.0718.

*4.3. (5E,9E)-methyl 9-methyl-2-(3-(2-methyl-1,3-dioxolan-2-yl)propanoyl)pentadeca-5,9-dien-13-ynoate (**26**)*

Homoallyl bromide **12** (357 mg, 1.33 mmol, 1.0 equiv., prepared as described above) was added to a solution of β-keto ester **25**[31] (430 mg, 1.99 mmol, 1.5 equiv) and cesium carbonate (562 mg, 1.73 mmol, 1.3 equiv) in acetone. The reaction vessel was then sealed and heated at 70 °C for 8 h, then cooled to rt and partitioned between ethyl acetate and half-saturated aqueous ammonium chloride. The aqueous layer was then extracted 3 times with ethyl acetate, and the combined organics were washed with water, brine, dried over sodium sulfate and concentrated using a rotary evaporator. The crude material was then purified using column chromatography with 15% ethyl acetate / hexanes to give 357 mg (73% yield) of β-keto ester **26** as a colorless liquid: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.48-5.26 (m, 2H), 5.16 (t, 1H, J=6.5), 3.97-3.86 (m, 4H), 3.71 (s, 3H), 3.49 (t, 3H, J=7.2), 2.68-2.62 (m, 2H), 2.22-1.84 (m, 14H), 1.77 (t, 3H, J=2.9), 1.59 (s, 3H), 1.30 (s, 3H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.7, 170.3, 135.89, 131.8, 128.4, 123.2, 109.1, 79.2, 75.4, 64.7, 64.6, 58.0, 52.3, 39.5, 36.7, 32.5, 31.1, 30.3, 28.0, 27.7, 23.9, 19.2, 16.0, 3.5 **HRMS** (ESI^+) Calcd. for $C_{24}H_{36}O_5Na$: 427.2460, found: 427.2457.

*4.4. 3-Methyl-2-((3E,7E)-7-methyltrideca-3,7-dien-11-yn-1-yl)cyclopent-2-enone (**2**)*

A solution of β-keto ester **26** (310 mg, 0.77 mmol, 1.0 equiv.), 2 mL of methanol, 2 mL of THF, and 2 mL of 2M KOH was heated at reflux for 3 h in a 75 °C oil bath and then allowed to cool to rt. The resulting mixture was partitioned between ethyl acetate and satd. ammonium chloride. The aqueous layer was extracted with 3 portions of ethyl acetate, and the combined organics were washed with water and brine, dried over sodium sulfate, and concentrated using a rotary evaporator. The crude mixture was then dissolved in 3.0 mL of methanol and treated with 0.5 mL of 2 M HCl. This mixture was stirred for 3 h then diluted with 2.5 mL of 2M KOH and 3 mL of THF. The resulting mixture was heated at reflux overnight, then allowed to cool to rt and partitioned between satd. ammonium chloride and ethyl acetate. The aqueous layer was extracted 3 times with ethyl acetate, and the organics were washed with water, brine, dried over sodium sulfate, and concentrated using a rotary evaporator. The crude material was purified using column chromatography (10 % ethyl acetate / hexanes) to give 155 mg (71%) of trienyne **2** as a colorless oil. Characterization data for trienyne **2** matched literature data:[14] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.47-5.30 (m, 2H), 5.16 (t, 1H, *J*=6.1), 2.48 (d, 2H, *J*=4.2), 2.36 (t, 2H, *J*=4.2), 2.32-1.92 (m, 15 H), 1.78 (t, *J*=2.3), 1.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 209.6, 170.6, 140.0, 136.0, 130.7, 129.4, 123.1, 79.2, 75.4, 29.6, 34.3, 31.5, 31.2, 31.1, 27.7, 23.2, 19.2, 17.3, 16.1, 3.5. **HRMS** (ESI^+) Calcd. for $C_{20}H_{28}ONa$: 307.2038, found: 307.2030.

Acknowledgments

This work was supported by an FSU GAP Award. The authors thank Prof Jacob Vanlandingham (FSU College of Medicine) for stimulating discussions and support of this research.

References and notes

1. Wei, J.; Xiao, G. *Acta Pharm. Sinica* **2013**, *34*, 1485-1490.
2. Cooke, P. S.; Nanjappa, M. K.; Yang, Z.; Wang, K. K. W. *Front. Neurosci*. **2013**, *7*, 108.
3. Deutsch, E. R.; Espinoza, T. R.; Atif, F.; Woodall, E. K. J.; Wright, D. W. *Brain Res.* **2013**, *1530*, 82-105.
4. Kaore, S. N.; Langade, D. K.; Yadav, V. K.; Sharma, P. T.; Vijay, R.; Sharma, R. *J. Pharm. Pharmacol*. **2012**, *64*, 1040-1062.
5. Guennouna, R.; Meffrea, D.; Labombarda, S. L.; Gonzalez, M. C; Gonzalez, D.; Stein, D. G.; De Nicola, A. F.; Schumacher, M. *Brain Res. Rev.*, **2008**, 493-505.
6. Meffre, D.; Labombarda, F.; Delespierre, B.; Chastre, A.; De Nicola, A. F.; Stein, D. G.; Schumacher, M.; Guennoun, R. *Neuroscience*, **2013**, *231*, 111-124.
7. Wright, D. W.; Yeatts, S. D.; Silbergleit, R.; Palesch, Y.Y.; Hertzberg, V. S.; Frankel M.; Goldstein, F. C.; Caveney, A. F.; Howlett-Smith, H.; Bengelink, E. N.; Manley, G. T.; Merck L. H.; Janis, L. S.; Barsan, W. G.; *N. Engl. J. Med.* **2014**, *371*, 2457-2466.
8. VanLandingham, J. W.; Cutler, S. M.; Virmani, S. H.; Covey, S. W.; Krishnan, D. F. K.; Hammes, S. R.; Jamnongjit, M.; Stein, D. G. *Neuropharmacology* **2006**, *51*, 1078-1085.
9. Vanlandingham, J. W.; Suber, J.; Marin, V.; Lewandowski, M. Prophylactic and post-acute use of progesterone to better outcomes associated with traumatic brain injury and concussion. PCT Int. Appl., WO 2013052849 A2, April 11, 2013.
10. Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732-2736.
11. Auchus, R. J.; Sampath, K. A.; Andrew, B. C.; Gupta, M. K.; Bruce, K. R.; Nigam P.; Covey, D. F. *Arch. Biochem. Biophys.* **2002**, *409*, 134-144.
12. Levy, D. E.; Zhang, F.; Zhan, X. Synthesis of ent-progesterone and intermediates thereof. PCT Int. Appl., WO 2015095339 A1, June 25, 2015.
13. Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332-4334.
14. Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274-4282.
15. Cran, J. W.; Han, Y.; Zhang, F. Synthesis of *ent*-progesterone and intermediates thereof. PCT Int. Appl., WO 2014145302 A2, September 18, 2014.
16. Nicolaou K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*, VCH: Weinheim, 1996.
17. Although bromide **8** is now commercially available, in the original publication by Johnson it was prepared in 2 steps – an addition of propyne to ethylene oxide and subsequent exchange of alcohol to bromide. The most cost-effective way to access **8** today, however

is from the corresponding alcohol according to Fuchs, M.; Fürstner, A. *Angew. Chem. Int. Ed.* **2015**, *54***,** 3978–3982.
18. The overall yield for a linear sequence is calculated by assuming no loss of material between steps (e.g., consumed by analytical methods) and, when a range of yields is provided for a particular step, using the high end of the yield range. The calculated overall yield thus represents a high-end estimate of what might be observed in practice and is therefore qualified as "up to" the calculated value. The yield of steps to prepare **8** is not included due to the lack of details in original publication.
19. Van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490–2491.
20. Clausen, D. J.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 5178 – 5181.
21. Cabezas J. A.; Pereira, A. R.; Amey, A. A. *Tetrahedron Lett.* **2001**, *42*, 6819–6822.
22. Nagano, H.; Sugihara, H.; Harada, N.; Fukuchi, N.; Yamada, K.; Izawa, H.; Shiota, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3560-3565.
23. Pospíšil, J. *Tetrahedron Lett.* **2011**, *52*, 2348–2352.
24. Julia, M. *Bull. Soc. Chim. Fr.* **1961**, 1849–1853.
25. McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566-2570.
26. Moiseenkov, A. M.; Czeskis, B. A.; Ivanova, N. M.; Nefedov, O. M. *J. Chem. Soc. Perkin 1* **1991**, 2639 – 2649.
27. Johnson, W. S.; William, D. G.; Lyle, T. A.; Mineo, N. *J. Am. Chem. Soc.* **1980**, *102*, 7800 – 7802.
28. Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem.* **1994**, *59*, 6150 – 6152.
29. Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504 – 515.
30. Johnson W. S.; Bartlett W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke G. R.; Bancroft, K. J.; *J. Org. Chem.* **1999**, *64*, 9587 – 9595.
31. Bahman, N.; Elmer, O. S.; Crabbe, P. *J. Chem. Soc. Perkin 1* **1983**, 2337 – 2347.
32. Zheng Y. F.; Dharmpal, S. D.; Allan, C. O. *Tetrahedron*, **1995**, *18*, 5255–5276.

Supplementary Material

Experimental procedures for alternative processes and ^{1}H NMR and ^{13}C NMR spectra.