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Nature-Inspired Tetrahydropentalene Building Blocks: Scalable Synthesis for Medicinal Chemistry Needs

Abstract

Inspired by the bioactivity of natural compounds with a bicyclo[3.3.0]octane core, the study focuses on developing tetrahydropentalene-2,5-dione (2,5-THP-dione) derivatives as potential building blocks for the use in medicinal chemistry. Using the commercially available 2,5-THP-dione, a number of alkylated derivatives and a monofunctional ketone were synthesized. Using optimized protocols for synthesis, target compounds were obtained with high yields on a multigram scale. These compounds are promising derivatives for further chemical derivatization and therapeutic use, and thus highlight the value of 2,5-THP-dione in creating complex molecular structures for drug discovery, as well as the importance of tetrahydropentalene derivatives as valuable building blocks in synthetic chemistry.

Keywords: tetrahydropentalene; building blocks; medicinal chemistry; multigram synthesis

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Білдинг-блоки на основі тетрагідропенталену, інспіровані природою: масштабований синтез для потреб медичної хімії

Анотація

Пропоноване дослідження, інспіроване біоактивністю природних сполук із біцикло[3.3.0]октановим ядром, зосереджено на розробці похідних тетрагідропентален-2,5-діону (2,5-THP-діону) як потенційних білдинг-блоків для застосування в медичній хімії. Використовуючи комерційно доступний 2,5-THP-діон, синтезували ряд його алкілованих похідних, а також монокето-похідну. Використовуючи оптимізовані протоколи синтезу, одержали цільові сполуки з високими виходами у мультиграмових кількостях. Синтезовані сполуки є перспективні похідні для подальшої хімічної дериватизації та терапевтичного застосування, що засвідчує цінність 2,5-THP-діону для створення складних молекулярних структур у процесі розроблення ліків, а також важливість похідних тетрагідропенталену як білдинг-блоків у синтетичній хімії.

Ключові слова: тетрагідропентален; білдинг-блоки; медична хімія; багатограмовий синтез

∎ Introduction

The quest to harness the potential of tetrahydropentalene (THP) derivatives in medicinal chemistry is driven by the remarkable biological activities observed for natural products featuring the bicyclo[3.3.0]octane core, such as carbacyclin (**1, Figure**), and clinprost (**3**). These compounds show prostaglandin analogs and platelet aggregation inhibitory properties, along with others displaying the anticancer activity like cylindramide (**2**), and antibiotic potential like geodin A (**4**). In general, they exemplify the diverse biological actions – from antimicrobial to enzyme-inhibiting activities – that THP structural motif offers [1]. The synthetic analogs of tetrahydropentalenes, thus, emerge as formidable scaffolds in the drug development, opening the opportunities for finding new therapeutic agents capable of targeting a broad spectrum of diseases.

The known synthetic biologically active bicyclo[3.3.0]octane derivatives were found to be potent dipeptidyl peptidase 4 (DPP-4) inhibitors for managing type 2 diabetes [2]. Meanwhile, the research of *Mitcheltree et al.* into bicyclic inhibitors of human arginase for cancer immunotherapy further exemplifies the potential of these derivatives in combatting severe health conditions [3].

In the realm of medicinal and synthetic chemistry, tetrahydropentalene derivatives stand out not only for their significant biological activity, but also for their versatility as intermediates. The synthetic routes towards biologically active tetrahydropentalene derivatives employ modern organic chemistry methods in search of potent THP-based compounds. The development of functionalized pentalenes *via* carbonyl-ene reactions and enzymatic kinetic resolution exemplifies the creative approaches undertaken to access these elusive compounds [4]. Additionally, the synthesis of racemic 1-desoxyhypnophilin underlines the utility of tetrahydropentalene derivatives in constructing complex natural products [5], demonstrating the structural and synthetic versatility of this class of compounds.

An in-depth review of the methodologies used for synthesizing tetrahydropentalene derivatives reveals a dynamic landscape marked by both tradition and novelty [1]. Each strategy offers unique advantages, such as enhanced yields and selectivity, yet often contends with the need for specialized reagents and stringent conditions, reflecting the evolving sophistication in the tetrahydropentalene synthesis.

However, it is safe to consider readily available tetrahydropentalene-2,5-dione (2,5-THP-dione) as the foundational material for the synthesis of tetrahydropentalene-based building blocks. Besides the fact that 2,5-THP-dione is a commercial bulk chemical, in our previous studies on the synthesis of bis-nor adamantane (stellane) and nor-adamantane derivatives [6, 7] we managed to adjust the literature protocol [8] for 2,5-THP-dione multikilo preparation. By leveraging the readily available and chemically versatile nature of 2,5-THP-dione, we devised a scalable synthesis approach facilitating the production of these compounds at multigram scales with yields ranging from good to excellent. Our study not only confirms the integral role of 2,5-THP-dione in fostering the synthesis of complex molecular structures, but also enhances the arsenal available for drug discovery and synthetic chemistry. Our efforts delineate a pathway for exploiting a broader spectrum of therapeutic and synthetic opportunities presented by tetrahydropentalene derivatives in the realm of medicinal chemistry and drug development.

∎ Results and discussion

Armed with an ample supply of 2,5-THP-dione, we embarked on synthesizing derivatives poised for a significant impact in future derivatization, carefully considering aspects, such as heavy atom
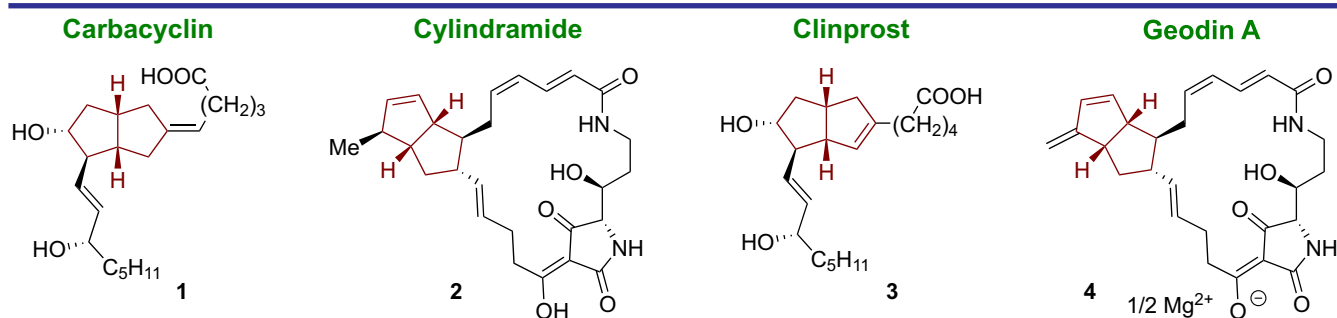

Figure. Some notable natural compounds with tetrahydropentalene core: carbocyclin (**1**), cyinderamide (**2**), clinprost (**3**), geodin A (**4**)

count and functional group distribution. Our selection included both di- and mono-functionalized derivatives, each chosen for its potential to enrich the chemical space of medicinal chemistry-relevant molecules. This choice was driven by the aim to harness the most valuable derivatives for the subsequent transformation, with an eye towards efficiency and scalability – the tactics that notably diverges from the more traditional approaches documented in the literature.

The synthetic studies began with compound **5**, going through its simple reaction with 2,2-dimethylpropanediol-1,3 under the PTSA catalysis in toluene to give compound **6** with a yield of 96% on the scale of over 40 grams per operation, thus simplifying the protocol and sidestepping the cumbersome separations that typically encumbered this transformation [9] (**Scheme**). The transition to compound **7** *via* reacting **6** with methylenetriphenylphosphorane "set the stage" for the synthesis of a suite of alkylated THP-ketones, including the previously unavailable methyl ketone **9** and tetrahydro-1'*H*-spiro[cyclopropane-1,2'-pentalen]-5'(3'*H*)-one **11** [10]. Methyl ketone **9** was synthesized through the series of transformations included a catalytic hydrogenation step utilizing palladium on activated charcoal under ambient conditions and the subsequent acid-mediated deprotection with a combined near-quantitative yield. Taking advantage of our previously developed in-flow diazomethane generation method [11], the transformation of compound **7** was carried out with diazomethane in the presence of palladium(II) acetate to obtain spiro-cyclopropane derivative **10** with a yield of 95%. It highlights this modern approach to the cyclopropanation of olefines and exhibits simplified and safer method for the synthesis of **10** compared to the previously described one [12]. The following acidic hydrolysis of compound **10** led to compound **11** with a yield of 88% on 22 g scale, further demonstrating the scalability and preparative potential of our synthesis strategies.

The next step was shifted to the transformation of compound **6**, which underscore the selective mono-reduction of the ketone group either to respective alcohol or hydrocarbon, opening opportunities for a broader THP core derivatization. The reduction of ketone **6** with the sodium borohydride powder in aprotic conditions (THF media) gave 12 grams of intermediate alcohol **12** with a yield of 79% (**Scheme**). The deprotection of compound **12** resulted in ketoalcohol **13** as a single diastereomer (*see* SI file for spectral details).

The use of a standard methylation protocol made it possible to obtain methoxyketone **14** with a yield of 91%. Products **13** and **14** are valuable THP-derived building blocks as both are individual diastereomers with two separately derivatizable functional groups. The reduction of keto-group in **6** to -CH$_2$- was achieved using the standard Wolff–Kishner reduction [13] protocol with hydrazine hydrate in ethylene glycol, followed by the addition of potassium hydroxide, resulting in ketal **15**, which then was subjected to the acidic hydrolysis and yielded desired ketone **16** quantitatively across two steps (**Scheme**). In the case of product **16** we were able to achieve significantly elevated yields on a larger scale compared to the literature [14].

Our research successfully demonstrates the synthesis of a series of target tetrahydropentalene derivatives, including alkylated monofunctional compounds **9** and **11**, bifunctional derivatives **13** and **14**, and the monofunctional ketone **16**. Each compound, valuable in its unique way, represents a significant contribution to the field of medicinal chemistry and synthetic organic chemistry. By carefully modifying existing protocols, we have not only increased the efficiency of these syntheses, but also achieved them on a multigram scale, thereby demonstrating the scalability of our approaches. The high yields obtained for these compounds once again underline the effectiveness of our improved methodologies. It is also noteworthy that all the compounds synthesized resemble *cis*-configuration, which is typical for THP-derivatives, and additionally verified by 2D-NMR studies (*see SI file for details*) Taken together, these results highlight the potential of our building blocks synthesized for further derivatization and research within the THP-derived chemical space.

■ Conclusions

In our study of tetrahydropentalene-2,5-dione derivatives, inspired by the rich biological activity of natural bicyclo[3.3.0]octane compounds, we successfully synthesized a suite of alkylated and functional derivatives. Using commercially available 2,5-THP-dione as a key starting material, we streamlined the synthetic protocols, achieving scalable production with significant yields. This approach not only facilitated the preparation of the compounds important for medicinal chemistry, but also demonstrated the versatility of 2,5-THP-dione as a precursor. Our findings,
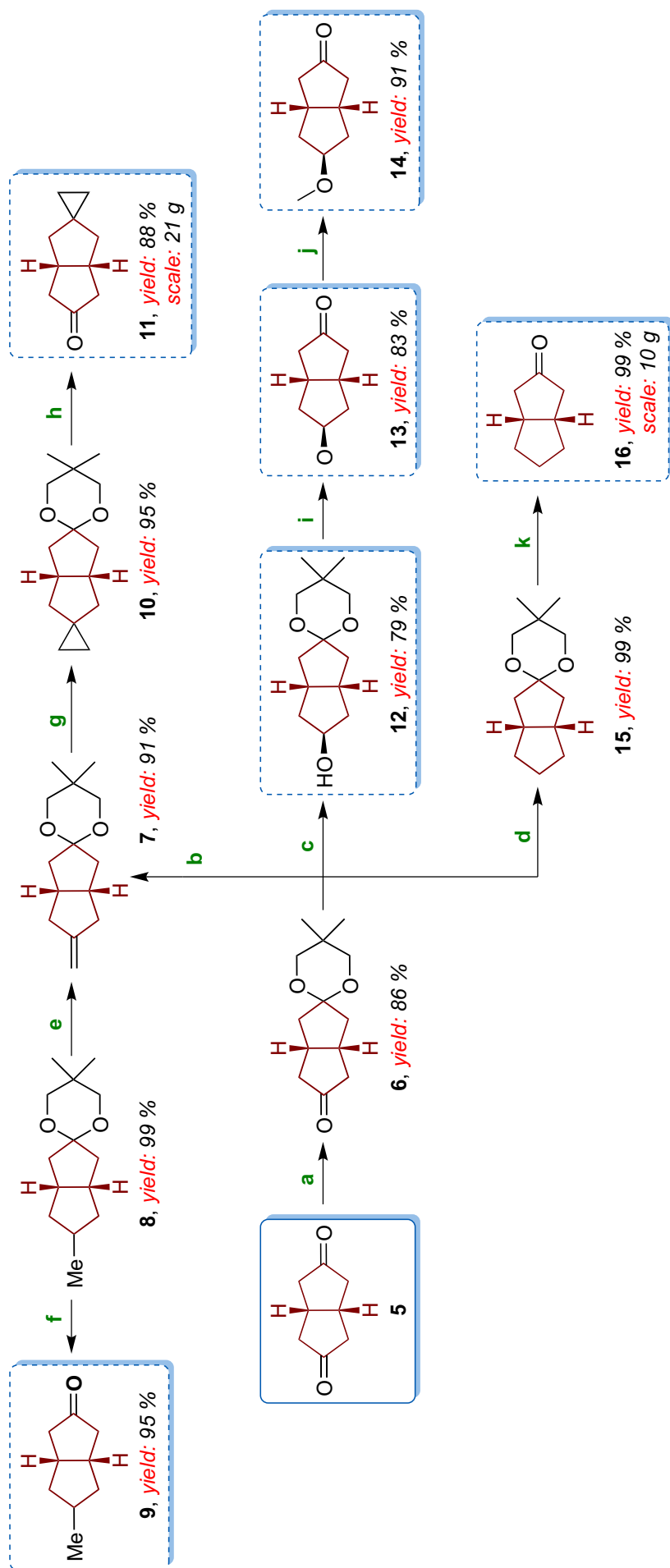
Scheme. The derivatization of tetrahydropentalene-2,5(1*H*,3*H*)-dione (**5**). *Experimental conditions:* (**a**) toluene/2,2-dimethyl-1,3-propanediol/*p*-TSA, 130 °C, 3 h; (**b**) THF/Ph₃P=CH₂, 0 °C to r.t., overnight; (**c**) THF/NaBH₄ (powder), –30 °C to r.t., overnight; (**d**) MEG/NH₂NH₂*H₂O, 90 °C, 2 h; KOH, 150 °C, 1 h; (**e**) MeOH, Pd/C (10%), H₂, r.t., overnight; (**f**) THF/H₂O, HCl (conc.), LiCl, r.t., overnight; (**g**) DCM, Pd(OAc)₂, CH₂N₂, r.t., 1 h; (**h**) THF/H₂O, HCl (conc.), LiCl, r.t., overnight; (**i**) THF/H₂O, HCl (conc.), LiCl, r.t., overnight; (**j**) MeCN, K₂CO₃, MeI, 40 °C, 18 h; (**k**) THF/H₂O, HCl (conc.), LiCl, r.t., overnight

marked by methodological innovation, efficiency and scalability, contribute significantly to the THP-derivatives pool available for wide derivatization and use in drug discovery projects, as well as demonstrate the essential role of tetrahydropentalenes in advancing synthetic chemistry and highlight their potential as valuable building blocks in the search for new therapeutic agents.

■ Experimental part

General information and materials

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on the automated melting point system. NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C nucleus) and Varian Unity Plus 400 spectrometers (at 400 MHz for ^{1}H, 101 MHz for ^{13}C nucleus). Tetramethylsilane (^{1}H, ^{13}C) was used as an internal standard. GCMS analyses were performed using an Agilent 5890 Series II 5972 GCMS instrument (electron impact (EI) ionization (70 eV)). Column chromatography was performed with silica gel (200-300 mesh). The elemental analysis was carried out in the Analytical Laboratory of the Institute of Organic Chemistry, NAS of Ukraine.

Experimental protocols
(3a*R*,6a*S*)-5',5'-Dimethyltetrahydro-1*H*-spiro[pentalene-2,2'-[1,3]dioxan]-5(3*H*)-one (6)

Compound **5** (30 g, 217.12 mmol), 2,2-dimethylpropanediol-1,3 (22.6 g, 217.12 mmol) and *p*-TSA (1.87 g, 0.05 equiv) were dissolved in toluene (500 mL). The mixture obtained was heated to 130 ^{o}C and stirred at this temperature with a Dean-Stark water trap. In 3 h it was cooled to room temperature and washed with Na$_2$CO$_3$ (200 mL, 10% aq. solution). The toluene layer was separated, dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. A crude material was purified by flash column chromatography (FCC) using EtOAc in hexane (0–50% gradient) as an eluent to give compound **6** as a colorless solid.

Yield – 41.7 g (86%). M. p. 42–46 ^{o}C. Anal. Calcd for C$_{13}$H$_{20}$O$_3$, %: C 69.61, H 8.99. Found, %: C 69.81, H 8.87. ^{1}H NMR (500 MHz, DMSO-d_6): δ, ppm: 0.86 (6H, s), 1.68–1.76 (2H, m), 1.95–2.03 (2H, m), 2.10–2.18 (2H, m), 2.33–2.44 (2H, m), 2.70 (2H, td, *J* = 8.7, 4.7 Hz), 3.36 (2H, s), 3.39 (2H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 22.1, 29.6, 36.0, 40.7, 44.0, 71.0, 71.1, 109.1, 219.0. GC-MS (EI), *m/z*: 224.2 [M]$^{+\cdot}$.

(3a*R*,6a*S*)-5',5'-dimethyl-5-methylenehexahydro-1*H*-spiro[pentalene-2,2'-[1,3]dioxane] (7)

Compound **6** (41.7 g, 185.91 mmol) was dissolved in THF (300 mL) and added in a dropwise manner to a suspension of freshly prepared methylenetriphenylphosphorane (made from 122.7 g of methyltriphenylphosphonium iodide (1.5 equiv) cooled to 0 ^{o}C and 31.3 g of potassium *tert*-butoxide (1.5 equiv)). After the addition was complete, the resulting mixture was allowed to reach room temperature and left to stir at the given conditions overnight. Volatiles were removed *in vacuo*, the residue was treated with water (300 mL) and extracted with MTBE (3×250 mL). Combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. A crude material was passed through SiO$_2$ pad using MTBE as an eluent to give a crude compound **7** as a yellow oil.

Yield – 37.4 g (91%). ^{1}H NMR (400 MHz, CDCl$_3$), δ, ppm: 0.93 (8H, d, *J* = 7 Hz), 1.41–1.53 (3H, m), 1.96–2.04 (3H, m), 2.04–2.10 (1H, m), 2.22–2.34 (2H, m), 2.41 (2H, s), 2.47–2.57 (2H, m), 3.44 (dd, *J* = 16.9, 6.7 Hz, 5H), 4.79 (2H, s).

(3a*R*,6a*S*)-5,5',5'-trimethylhexahydro-1*H*-spiro[pentalene-2,2'-[1,3]dioxane] (8)

Compound **7** (5 g, 22.3 mmol) was dissolved in MeOH. Pd on activated charcoal (0.5 g, 10%) was added and the mixture obtained was evacuated and backfilled with hydrogen. The resulting suspension was stirred overnight at ambient temperature under H$_2$ atmosphere (balloon pressure). After that, the catalyst was filtered off, the filtrate was concentrated *in vacuo*, and the residue was used in further transformations with no additional treatment. ^{1}H NMR of the material obtained was not characteristic due to the partial deprotection of ketone and complexity of the spectrum. The yield was calculated as quantitive, ~5.1 g.

(3a*R*,6a*S*)-5-methylhexahydropentalen-2(1*H*)-one (9)

Compound **8** (5.1 g, the material from the previous step) was dissolved in a 1:1 mixture of THF (100 mL) and water (100 mL). Concentrated HCl (10 mL, 37% aq.), followed by 0.91 g of LiCl (22 mmol) was added. After the addition, the solution was allowed to stir at ambient temperature overnight. Volatiles were removed *in vacuo*. The residue was washed with MTBE (3×150 mL). Combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. A crude material was purified *via* FCC using MTBE in hexane (0–100% gradient) as an eluent to give compound **9** as a yellow oil.

Yield – 3.1 g (95%). Anal. Calcd for $C_9H_{14}O$, %: C 78.21, H 10.21. Found, %: C 78.32, H 10.27. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.79–1.56 (6H, m), 1.56–2.22 (6H, m), 2.40–2.56 (2H, m), 2.61–2.87 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ, ppm: 19.9, 20.0, 36.3, 38.9, 39.7, 42.4, 43.0, 44.9, 45.3, 221.2. GC-MS (EI), m/z: 138.1 [M]$^{+\cdot}$.

(3a'*R*,6a'*S*)-5",5"-Dimethyltetrahydro-1'*H*,3'*H*-dispiro[cyclopropane-1,2'-pentalene-5',2"-[1,3]dioxane] (10)

Compound **7** (37.4 g, 168.2 mmol) was dissolved in a solution of diazomethane (*ca.* 1 M) in DCM (250 mL). The mixture obtained was stirred with $Pd(OAc)_2$ (0.1 equiv) overnight. After a careful decomposition of the excessive diazomethane, it was concentrated *in vacuo* and passed through SiO_2 pad using MTBE as an eluent to give a crude compound **10** as a colorless oil used in the further step with no additional purification.

Yield – 35.7 g (*ca.* 95%). ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.29–0.52 (m, 8H), 0.94 (s, 6H), 1.27–1.30 (3H, m), 1.42–1.46 (3H, m), 1.62–1.82 (3H, m), 1.91–1.96 (3H, m), 2.17–2.22 (3H, m), 2.35 (1H, s), 2.47–2.63 (5H, m), 2.87 (3H, br. s), 3.49–3.51 (4H, m).

(3a'*R*,6a'*S*)-tetrahydro-1'*H*-spiro[cyclopropane-1,2'-pentalen]-5'(3'*H*)-one (11)

Compound **10** (35.7 g, 160 mmol) was dissolved in a 1:1 mixture of THF (300 mL) and water (300 mL). Concentrated HCl (30 mL, 37% aq.), followed by 6.7 g of LiCl (160 mmol) was added. After the addition, the mixture was allowed to stir at ambient temperature overnight. Volatiles were removed *in vacuo*; the residue was washed with MTBE (3×250 mL). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A crude material was purified *via* FCC using MTBE in hexane (0-100% gradient) as an eluent to give compound **11** as a yellow oil.

Yield – 21.1 g (88%). Anal. Calcd for $C_{10}H_{14}O$, %: C 79.96, H 9.39. Found, %: C 80.11, H 9.30. ^1H HNMR (500 MHz, $CDCl_3$), δ, ppm: 0.36–0.44 (2H, m), 0.45–0.53 (2H, m), 1.41 (2H, dd, J = 13.1, 4.4 Hz), 1.91 (2H, dd, J = 13.1, 7.8 Hz), 2.10–2.21 (2H, m), 2.48 (2H, ddd, J = 19.2, 7.3, 2.2 Hz), 2.86 (2H, tt, J = 8.7, 4.7 Hz). ^{13}C NMR (151 MHz, $CDCl_3$), δ, ppm: 11.2, 12.9, 22.1, 40.3, 42.6, 44.8, 220.9. GC-MS (EI), m/z: 150.1 [M]$^{+\cdot}$.

(3a*R*,5r,6a*S*)-5',5'-dimethylhexahydro-1*H*-spiro[pentalene-2,2'-[1,3]dioxan]-5-ol (12)

Compound **6** (15 g, 66.87 mmol) was dissolved in THF (300 mL), and this solution was cooled to -20–-30 °C. Then, dry $NaBH_4$ (2.54 g, 66.87 mmol) was added in portions, maintaining the internal temperature below -20 °C. After that, the mixture was allowed to slowly warm to room temperature and left to stir at the given conditions overnight. Then volatiles were removed *in vacuo*, the residue was treated with NH_4Cl (200 mL, 15% aq. solution) and extracted with MTBE (3×250 mL). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Compound **12** was obtained as a white solid.

Yield – 11.86 g (79%). M. p. 61–62 °C. Anal. Calcd for $C_{13}H_{22}O_3$, %: C 68.99, H 9.80. Found, %: C 69.08, H 9.85. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.82–1.11 (6H, m), 1.44–1.62 (2H, m), 1.86–1.97 (3H, m), 2.03–2.31 (4H, m), 2.44–2.84 (2H, m), 3.40–3.58 (4H, m), 4.14–4.46 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 21.32, 22.51, 30.07, 36.44, 37.76, 38.56, 40.80, 42.45, 42.93, 45.56, 71.59, 71.91, 72.18, 74.72, 75.58, 110.48. GC-MS (EI), m/z: 226 [M]$^{+\cdot}$.

(3a*R*,5r,6a*S*)-5-hydroxyhexahydropentalen-2(1*H*)-one (13)

Compound **12** (11.86 g, 52.47 mmol) was dissolved in a 1:1 mixture of THF (100 mL) and water (100 mL) and concentrated HCl (15 mL, 37%, aq.). After the complete dissolution, the mixture was allowed to stir at ambient temperature overnight. Volatiles were removed *in vacuo*; the residue was washed with EtOAc (5×75 mL). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A crude material was purified *via* FCC using MTBE in hexane (0–100% gradient) as an eluent to give compound **13** as a white solid.

Yield – 6.12 g (83%). M. p. 50–52 °C. Anal. Calcd for $C_8H_{12}O_2$, %: C 68.55, H 8.63. Found, %: C 68.43, H 8.72. ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.38 (2H, dt, J = 13.2, 4.4 Hz), 1.96 (2H, ddd, J = 13.4, 8.2, 5.6 Hz), 2.07 (2H, dd, J = 18.9, 3.4 Hz), 2.38–2.42 (1H, m), 2.42–2.46 (1H, m), 2.59–2.73 (2H, m), 4.07–4.17 (1H, m), 4.51 (1H, d, J = 3.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 37.6, 43.0, 45.6, 73.4, 220.2. GC-MS (EI), m/z: 140.1 [M]$^{+\cdot}$.

(3a*R*,5r,6a*S*)-5-methoxyhexahydropentalen-2(1*H*)-one (14)

Compound **13** (2 g, 14.3 mmol) was dissolved in MeCN (40 mL). Potassium carbonate (2.92 g, 21.45 mmol) and methyl iodide (3.05 g, 21.45 mmol) were added sequentially. The mixture obtained was stirred for 18 h at 40 °C. Then, it was cooled to room temperature, the insoluble substances were filtered off, and the filter cake was washed with an additional MeCN (10 mL) portion. The filtrate

was concentrated *in vacuo*, and the residue was passed through SiO_2 pad using MTBE as an eluent. The filtrate was concentrated *in vacuo* to give compound **14** as a colorless oil.

Yield – 2.01 g (91%). Anal. Calcd for $C_9H_{14}O_2$, %: C 70.10, H 9.15. Found, %: C 70.17, H 9.22. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.65 (2H, dt, $J = 13.8$, 4.0 Hz), 2.02–2.15 (2H, m), 2.21 (2H, dd, $J = 19.3$, 3.7 Hz), 2.43–2.55 (2H, m), 2.71–2.81 (2H, m), 3.24 (3H, s), 3.83–3.93 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 37.74, 39.19, 45.25, 56.39, 83.61, 220.46. GC-MS (EI), m/z: 154.1 $[M]^{+\cdot}$.

(3a*R*,6a*S*)-5',5'-dimethylhexahydro-1*H*-spiro[pentalene-2,2'-[1,3]dioxane] (15)

Compound **6** (10 g, 44.54 mmol) was dissolved in ethylene glycol (40 mL) and treated with 4 equiv of hydrazine hydrate (8.9 g). This mixture was stirred for 2 h at 90 °C and then treated with KOH (9.98 g, 178.16 mmol, 4.0 equiv). The mixture obtained was heated to 150 °C and stirred at the given conditions for 1 h (strong N_2 evolution was observed). Then, it was cooled to room temperature and diluted with water (100 mL). The aqueous mixture was extracted with MTBE (3×100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a crude product (the mixture contained the desired product, ethylene glycol and trace of the deprotected product). This mixture was then used with no additional treatment directly at the next step, the yield was calculated as close to quantitative.

(3a*R*,6a*S*)-hexahydropentalen-2(1*H*)-one (16)

A mixture containing compound **15** from the previous step was dissolved in a 1:1 solution of THF (100 mL) and water (100 mL) and concentrated HCl (15 mL, 37% aq.). After the complete dissolution of **15**, the mixture obtained was allowed to stir at ambient temperature overnight. Volatiles were removed *in vacuo*, and the residue was washed with Et_2O (3×100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. A crude material was purified *via* FCC using MTBE in hexane (0–100% gradient) as an eluent to give compound **16** quantitatively as a colorless oil.

Anal. Calcd for $C_8H_{12}O$, %: C 77.38, H 9.74. Found, %: C 77.27, H 9.70. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.33–1.46 (2H, m), 1.55–1.82 (2H, m), 1.85–2.06 (4H, m), 2.41–2.54 (2H, m), 2.58–2.76 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 25.5, 33.4, 39.6, 44.7, 221.2. GC-MS (EI), m/z: 124.1 $[M]^{+\cdot}$.

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