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Convenient and easy access to 2-hydroxycyclopent-2-enones from acylcyanohydrins

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ABSTRACT

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A convenient access to 2-hydroxycyclopentenones was designed from acylcyanohydrins, by using titanacyclopropane complexes as nucleophilic partners and an intramolecular aldol condensation in basic conditions. The development of a one-pot procedure allows a step- and atom-economic process, and the use of Grignard reagents other than ethylmagnesium bromide provided valuable 3,4-disubstituted 2-hydroxycyclopentenones. The utility of the hydroxy group was illustrated by further functionalization of the α -position using palladium-mediated cross-coupling reactions.

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1. Introduction

The cyclopenten-2-one moiety is found in several natural and synthetic compounds with organoleptic properties and biological activities. For instance, the well-known *cis*-jasmone (**1**) is a fragrant compound of jasmine flowers whereas its synthetic pyrethroid congener, allethrin I (**2**),¹ is used as the mixture of the 8 stereoisomers as household insecticides (Figure 1). The naturally occurring (+)-terrein (**3**) could also be cited for its interesting inhibition properties towards human tumor cell growth.² This scaffold can also display hydroxy function at the C2-position, as in Coronol[®] (**4**), a flavoring agent with caramel and maple notes.³ These 2-hydroxycyclopentenones, also referenced as cyclopentane-1,2-diones, can be part of natural products, like (±)-tylopilusins (**5a,b**)⁴ and (±)-suillusine (**6**),⁵ extracted from fruiting bodies of *Tylopilus eximius* and *Suillus granulatus* respectively, and are also used as synthetic intermediates, such as the polycyclic compound **7**, a precursor of the anticancer agent Rocaglamide.⁶

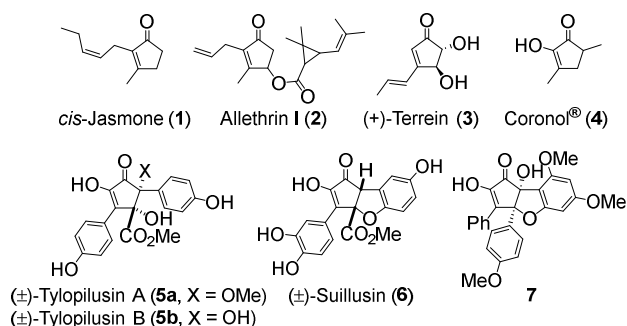


Fig. 1. Cyclopenten-2-ones and 2-hydroxycyclopenten-2-ones of interest

Due to their biological importance and their interest as building blocks, cyclopentenones represent an intensive research field, and biomass is an interesting renewable resource to prepare these cyclic enones by intramolecular or intermolecular Pincatelli rearrangement of furans,⁷ and furfuryl derivatives.⁸ The Pauson-Khand reaction, i.e. the [2+2+1] cycloaddition between an alkyne, an alkene and carbon monoxide is largely used in total syntheses,⁹ and variants consisting in titanium-mediated intramolecular coupling of alkynes with α,β -unsaturated esters or β -ketoesters were reported.¹⁰ An important alternative is the Nazarov cyclization of divinyl ketones, which is also able to provide 2-hydroxycyclopentenone derivatives when an enol equivalent or enol ether is conjugated to the ketone function.^{11,12} Cyclopentenones were also prepared by cyclization of 1,4-diketones,^{7,13} and this approach has already been applied to the synthesis of 2-hydroxycyclopentenones from carboxylic esters of 5-hydroxy-1,4-diketones, obtained from convergent synthesis involving a Stetter reaction with benzaldehydes, and using acidic conditions^{13a} or basic alcoholic media.^{13b-d} Very recently, an efficient Suzuki cross-coupling reaction between 3-bromo-cyclopentenones and arylboronic acids was reported to functionalize the cyclopentenone ring but the yields do not reach more than 26% when the 2-hydroxy group was not protected.¹⁴ Thus, if cyclopentenones are well described by several synthetic processes,⁷⁻¹³ the access to 2-hydroxy derivatives is more limited and such scaffold constitutes an interesting target for synthetic chemists.

In this context, we present a convenient two-step access to 2-hydroxycyclopenten-2-ones **9** from easily available acyl cyanohydrins **8** by taking the advantage of the previously published titanium-mediated formation of 5-hydroxy-1,4-

diketones from acylcyanohydrins.¹⁵ The subsequent improvement in a one-pot procedure affords a higher yielding and step-economic process and allows the formation of 3,4-disubstituted 2-hydroxycyclopentenones (Scheme 1).

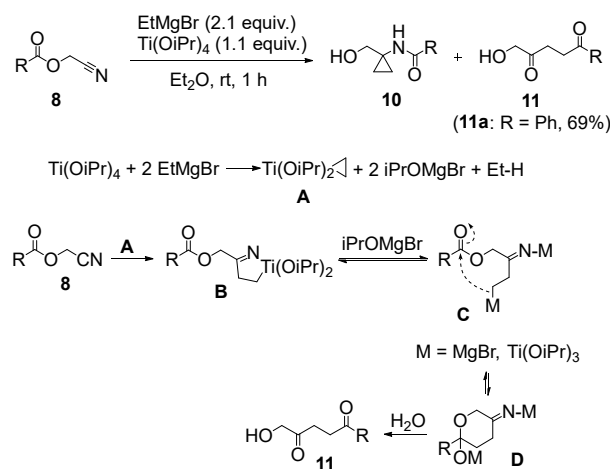


Scheme 1. One-pot synthesis of 2-hydroxycyclopentenones **9** from acylcyanohydrins **8**.

2. Results and discussion

2.1. Aldol condensation

The 5-hydroxy-1,4-diketones **11**, required for the formation of 2-hydroxycyclopentenones, are directly accessible from cyanohydrins derivatives **8** via the use of titanacyclopentane reagents, themselves generated from titanium isopropoxide and Grignard reagents (Scheme 2).¹⁵ In this reaction, the formal 1,2-dianion reactivity of titanacyclopentanes was modulated by the nature of the solvent. Indeed, by using Et₂O as solvent instead of THF, the formation of dicarbonyl compounds **11** is largely privileged over the cyclopropylamine derivatives **10**, and 5-hydroxy-1,4-diketones **11** were isolated in up to 74% yield (69% yield in the case of **11a**), after purification. From a mechanistic point of view, after insertion of the nitrile moiety of **8** into the titanacyclopentane complex **A**, the azatitanacyclopentene **B** would evolve into a C,N di-metallated intermediate **C** through a putative reversible equilibrium. The intramolecular cyclization by nucleophilic addition onto the ester function would afford the stable cyclic intermediate **D** that provides hydroxydiketones **11** after hydrolysis.

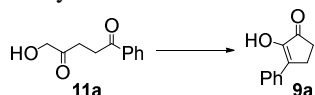


Scheme 2. Titanium-mediated synthesis of 5-hydroxy-1,4-diketones **11**.

The intramolecular cyclization of the 5-hydroxy-diketones was first carried out with the model compound **11a** and NaH as a base in Et₂O under argon (Table 1, entry 1). To our delight, the 2-hydroxycyclopentenone **9a** was obtained in 86% yield as the only product. Obviously, the hydroxy moiety does not interfere in the cyclization process, and competes with the related protocol involving methanolate-mediated intramolecular cyclization of the acetyl ester of **11a** (83% yield),^{13a} the latter being prepared by Stetter reaction. The use of K₂CO₃ in MeOH also led to complete conversion and good yield without purification, but required a longer reaction time (entry 2). In order to perform a one-pot reaction directly from the cyanohydrins **8** (i.e. without the

isolation of the diketones **11**, *vide infra*), aqueous media is required to hydrolyze the metallated imine intermediate **D** before performing base-mediated cyclization into **9**. A biphasic media was thus used with diketone **11a** in Et₂O and 3M NaOH solution in water. Under these conditions, the reaction was completed within 30 minutes, but the expected product was isolated in a lower 75% yield (entry 3). Benzoic acid and 4-oxo-4-phenylbutanoic acid were also obtained as by-products, suggesting an aerobic oxidation of the starting material in the basic reaction media.¹⁶ Consequently, the experiment was reiterated with carefully degassed aqueous solution of NaOH, affording cyclopentenone **9a** in 94% yield without purification (entry 4). The use of lower amounts of NaOH (1.5 equiv.) provided **9a** in similar yield but required longer reaction time (entry 5) and catalytic amount of NaOH (0.2 equiv) led only to 13% conversion after 3 days (entry 6), showing that at least one equiv of base is required. At last, weaker basic media was ineffective, since sodium hydrogen carbonate, ammonium hydroxide, sodium carbonate and disodium hydrogen phosphate aqueous solutions were tested without success (entries 7-10).

Table 1. Study of the base-mediated intramolecular cyclization of hydroxydiketone **11a**.



| Entry | Conditions | Solvent | Equiv. ^a | Time (h) | Conv. ^b | Yield ^c |
|-------|---|-------------------|---------------------|----------|--------------------|--------------------|
| 1 | NaH | THF | 1.1 | 3 | 100% | 86% |
| 2 | K ₂ CO ₃ | MeOH | 4 | 12 | 100% | 90% |
| 3 | NaOH 3M | Et ₂ O | 9 | 0.5 | 100% | 75% ^d |
| 4 | NaOH 3M ^e | Et ₂ O | 9 | 0.5 | 100% | 94% |
| 5 | NaOH 0.5M ^e | Et ₂ O | 1.5 | 3 | 100% | 90% |
| 6 | NaOH 0.1M ^e | Et ₂ O | 0.2 | 72 | 13% | - |
| 7 | Sat. NaHCO ₃ | Et ₂ O | - | 12 | 0 | - |
| 8 | NH ₄ OH 0.8M | Et ₂ O | 1.5 | 12 | 0 | - |
| 9 | Na ₂ CO ₃ 0.5M | Et ₂ O | 1.5 | 12 | 0 | - |
| 10 | Na ₂ HPO ₄ ^f | Et ₂ O | - | - | 0 | - |

^a Number of equivalents of base compared to the starting ketone **11a**. ^b Conversion was monitored by TLC and calculated by integration of ¹H NMR signals recorded for the crude residue. ^c Isolated yield. Unless specified, the product was isolated pure after work-up, without any further purification. ^d Purification by column chromatography was required. ^e The aqueous NaOH solution was freshly prepared and degassed before use. ^f Buffer pH 11 used.

2.2. One-pot synthesis of cyclopentenones

With the above optimized conditions in hand (3M aqueous degassed NaOH solution), the one-pot version was explored and compared to the two-step method (Table 2). At first, the diketones **11b-d** displaying methoxy, bromide and fluoride groups in the *para* position of the phenyl substituent were prepared in 60-65% yield from the parent acylcyanohydrins **8b-d**, after aqueous acidic workup and purification by chromatography on silicagel, according to reported procedure.^{15b} Subsequent cyclization in aqueous sodium hydroxide solution efficiently provided **9b-d**, giving access to cyclopentenones **9a-d** in 46-62% yields for the two-step preparation from nitriles **8a-d**.

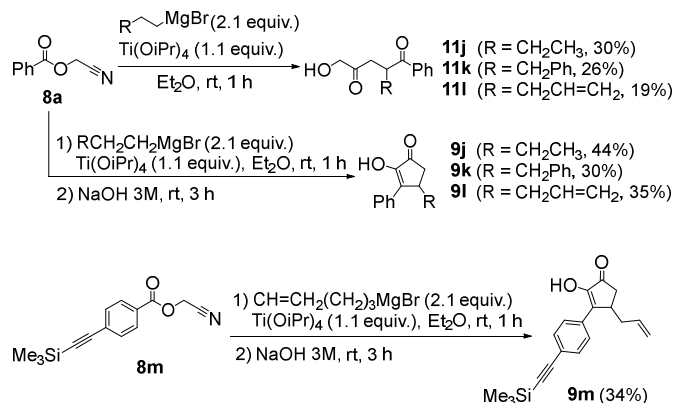
The one-pot method was then performed by adding a degassed NaOH 3M aqueous solution to the crude reaction mixture, obtained after addition of EtMgBr to the nitriles **8** and Ti(OiPr)₄ in Et₂O. After 3 h of additional stirring and work-up, the crude material was purified by chromatography on silicagel to afford the pure cyclopentenones **9a-d**. Apart from the simplicity of the procedure, the one-pot version was equivalent to the two-step procedure in terms of efficiency for the phenyl-substituted compound **9a**, even when the reaction was conducted on 12 mmol scale of **8a** (entry 1). On the other hand, a significantly better yield (78% instead of 49%) was obtained for the *para*-methoxy derivative **9b** by using the one-pot procedure (entry 2) and an increase of 27-28% in the yield was also observed for products **9c** and **9d** (entries 3 and 4). As a result, the one-pot process was found to outperform the two-step one. The main reason of this efficiency lies in the difficulty to purify the diketones by column chromatography in the two-step process.¹⁷ This one-pot method was next applied to the synthesis of other hydroxycyclopentenones from easily available acylcyanohydrins (entries 5-8). The reaction works well with aliphatic and alkenyl moieties, giving **9e-h** in 63-72% yields. The formation of **9i**, bearing an alkyne moiety was also possible but in lower yield (entry 9).

Table 2. Two-step versus one-pot preparation of cyclopentenones **9** from acylcyanohydrins **8**.

| Entry | R | Two-step 11 (Yield)/ 9 (Yield) | Two-step Yield | One-pot ^a Yield |
|-------|--|---|-------------------|-------------------------------|
| 1 | Ph | 11a (69%) / 9a (90%) | 9a (62%) | 9a (60%) ^b |
| 2 | <i>p</i> -MeO-Ph | 11b (65%) / 9b (75%) | 9b (49%) | 9b (78%) |
| 3 | <i>p</i> -Br-Ph | 11c (60%) / 9c (87%) | 9c (52%) | 9c (80%) |
| 4 | <i>p</i> -F-Ph | 11d (60%) / 9d (76%) | 9d (46%) | 9d (73%) |
| 5 | Me | - | - | 9e (72%) |
| 6 | <i>n</i> -Pr | - | - | 9f (68%) |
| 7 | <i>i</i> Bu | - | - | 9g (63%) |
| 8 | CH ₂ =CH-C ₈ H ₁₆ | - | - | 9h (69%) |
| 9 | Ph-C≡C | - | - | 9i (21%) |

^a One-pot procedure: after the addition of EtMgBr to a solution of 1 mmol of nitrile **8** and Ti(OiPr)₄ in Et₂O, the mixture was stirred for 1 h at room temperature. A 3M freshly prepared and degassed aqueous NaOH solution was then added under argon and vigorous stirring was maintained for further 3 h. ^b Reaction undertaken on 12 mmol of substrate **8a** (the yield was 64% when 1 mmol of **8a** was used).

The use of substituted ethyl Grignard reagents gives the opportunity to further functionalize the cyclopentenones (Scheme 3). Interestingly, even though the corresponding diketones **11j-l** were isolated in modest yields in the above Ti-mediated reaction, they were obtained as a single regioisomer.^{15a} Here also, the one-pot formation of hydroxycyclopentenones increases the overall yield of the transformation, providing 3,4-disubstituted 2-hydroxycyclopentenones **9j-l**. Furthermore, the synthetic applicability was well illustrated by the formation of the multifunctional scaffold **9m**, in only one step from nitrile **8m**.

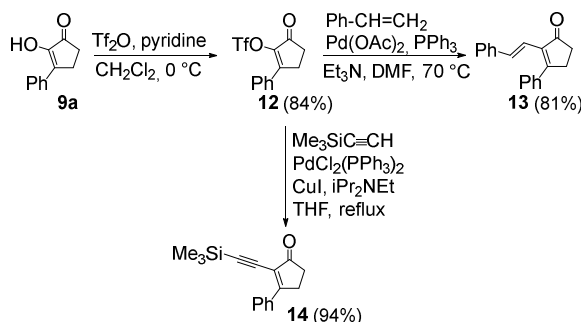


Scheme 3. Synthesis of substituted cyclopentenones

2.3. Functionalization of cyclopentenones

The hydroxy moiety of the prepared cyclopentenones can be used for further modifications, as exemplified below by palladium-mediated cross-coupling reactions (Scheme 4).

The compound **9a** was selectively converted into the corresponding triflate **12** by using trifluoromethanesulfonyl anhydride. The subsequent Heck reaction with styrene was performed under standard conditions to afford the dienone **13** in good yield.¹⁸ Alternatively, the Sonogashira coupling of **12** was performed with trimethylsilylacetylene and $\text{PdCl}_2(\text{PPh}_3)_3$ in THF to afford the enynone **14** in excellent yield.



Scheme 4. Cross-coupling reactions with triflate derivative of **9a**.

3. Conclusion

A general synthesis of 2-hydroxycyclopentenone derivatives was presented, based on the titanium-mediated conversion of easily available acyl cyanohydrins to 5-hydroxy-1,4-diketones, followed by a selective basic cyclization. The direct formation of the cyclopentenones without prior purification of the diketone (one-pot method) was proven to be more efficient. The scope of the reaction was explored, allowing the straightforward synthesis of 3,4-difunctional 2-hydroxycyclopentenones, and, by modification of the 2-hydroxy moiety, the preparation of 2,3-disubstituted cyclopentenones.

4. Experimental section

4.1. General remarks

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under argon. Et_2O , THF and CH_2Cl_2 were purified by passing through neutral alumina columns under nitrogen. DMF and Et_3N were distilled under argon before use. The Grignard reagents were prepared in anhydrous Et_2O using the conventional method from the

appropriate bromide precursors and Mg turnings, and the resulting solutions were titrated before use according to the B. E. Love method.¹⁹ The commercially available chemical reagents were purchased from Sigma-Aldrich and used without purification. The aqueous NaOH solution used for the cyclization of diketones was freshly prepared from ultrapure water purified on Milli-Q® system and was degassed before use.

Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) with detection using ethanolic potassium permanganate solution. Column chromatographies were carried out using silica gel 60 (0.040-0.063 mm) from Merck. Melting points were determined with a Büchi B-540 melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 or Bruker AC-400 spectrometer. Chemical shifts (δ) are expressed in ppm units, relative to the residual solvent peak. Coupling constants are given in Hz. The multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quadruplet (q), apparent sextuplet (app sx), apparent nonuplet (app non), multiplet (m), and broad signal (bs). IR spectra were obtained on a Perkin Elmer Spectrum One spectrometer on a single-reflection diamond ATR unit. High resolution mass spectra were recorded on a Waters Micromass GCT Premier spectrometer. Acylcyanohydrins **8a-d**,^{15b} **8e**,²⁰ **8f-i**,^{15b} and 1,4-diketones **11a-d**,^{15a} were prepared according to previously reported procedures.

4.2. General one-pot procedure to access cyclopentenones **9**

To a solution of the appropriate acylcyanohydrin **8** (1 mmol) in Et_2O (5 mL) cooled to 0 °C was added $\text{Ti}(\text{OiPr})_4$ (327 μL , 1.1 mmol). A solution of the appropriate Grignard reagent in Et_2O (2.1 mmol) was added dropwise over a period of 15 min and the mixture was allowed to warm up to room temperature. After stirring at room temperature for 1 h, a 3M freshly prepared and degassed aqueous NaOH solution (3 mL) was added under argon and vigorous stirring was maintained for further 3 h. The solution was acidified by adding a 3M HCl aqueous solution. The aqueous phase was extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with brine, and dried over MgSO_4 . After filtration, the organic fraction was concentrated under reduced pressure and the crude residue was purified by flash chromatography on silica gel to afford the pure cyclopentenone **9**.

4.2.1. 2-Hydroxy-3-phenylcyclopent-2-enone (**9a**)^{13b}

Prepared from acylcyanohydrin **8a** (12 mmol) and EtMgBr . Purification by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9a** (1.25 g, 60%) as a beige solid; mp = 188–190 °C (lit: 187–189 °C). ^1H NMR (200 MHz, CDCl_3): δ (ppm) 7.93 (m, 2H), 7.53–7.36 (m, 3H), 6.40 (bs, 1H), 2.95–2.86 (m, 2H), 2.62–2.55 (m, 2H). ^{13}C NMR (50 MHz, CDCl_3): δ (ppm) 203.1, 148.4, 138.1, 134.1, 129.6, 128.8, 127.8, 31.2, 23.5.

4.2.2. 2-Hydroxy-3-(4-methoxyphenyl)cyclopent-2-enone (**9b**)^{13c}

Prepared from acylcyanohydrin **8b** and EtMgBr . Purification by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9b** (159 mg, 78%) as a yellow solid; mp = 186–188 °C (lit: 200–201 °C). ^1H NMR (200 MHz, CDCl_3): δ (ppm) 7.89 (m, 2H), 6.97 (m, 2H), 6.12 (s, 1H), 3.87 (s, 3H), 2.90–2.83 (m, 2H), 2.59–2.53 (m, 2H). ^{13}C NMR (50 MHz, CDCl_3): δ (ppm) 202.7, 160.7, 147.2, 138.8, 129.6, 126.9, 114.2, 55.5, 31.1, 23.6.

4.2.3. 2-Hydroxy-3-(4-bromophenyl)cyclopent-2-enone (**9c**)

Prepared from acylcyanohydrin **8c** and EtMgBr. Purification by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9c** (202 mg, 80%) as a pale yellow solid; mp = 200–202 °C. IR (neat): $\tilde{\nu}$ = 3201, 2921, 2884, 1699, 1633, 1583, 1485, 1448, 1384, 1272, 1204, 1133, 1072 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ (ppm) 7.79 (m, 2H), 7.58 (m, 2H), 6.49 (bs, 1H), 2.90–2.84 (m, 2H), 2.61–2.55 (m, 2H). ^{13}C NMR (50 MHz, CDCl_3): δ (ppm) 202.8, 148.6, 136.6, 132.9, 132.0, 129.3, 123.9, 31.1, 23.4. HRMS (CI- CH_4/NH_3): calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{Br}$ [$\text{M} + \text{H}$] $^+$ 252.9864; found 252.9869.

4.2.4. 2-Hydroxy-3-(4-fluorophenyl)cyclopent-2-enone (**9d**)^{13c}

Prepared from acylcyanohydrin **8d** and EtMgBr. Purification by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9d** (141 mg, 73%) as a beige solid; mp = 176–178 °C (lit: 177–178 °C). ^1H NMR (200 MHz, CDCl_3): δ (ppm) 7.92 (m, 2H), 7.14 (m, 2H), 6.33 (s, 1H), 2.91–2.84 (m, 2H), 2.62–2.55 (m, 2H). ^{13}C NMR (50 MHz, CDCl_3): δ (ppm) 203.1, 163.3 (d, $J_{\text{C-F}}$ = 251.0 Hz), 148.1, 137.4, 130.4 (d, $J_{\text{C-F}}$ = 3.4 Hz), 129.8 (d, $J_{\text{C-F}}$ = 8.3 Hz), 115.8 (d, $J_{\text{C-F}}$ = 21.6 Hz), 31.2, 23.6.

4.2.5. 2-Hydroxy-3-methylcyclopent-2-en-1-one (**9e**)²¹

Prepared from acylcyanohydrin **8e** and EtMgBr. Purification by flash chromatography on silica gel (20% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9e** (81 mg, 72%) as a white solid; mp = 102–104 °C (lit: 103–105 °C). IR (neat): $\tilde{\nu}$ = 3320, 2918, 1704, 1644, 1402, 1208, 1115, 959 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 6.57 (bs, 1H), 2.44–2.34 (m, 4H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 203.4, 149.3, 145.1, 32.1, 27.3, 14.4.

4.2.6. 2-Hydroxy-3-propylcyclopent-2-en-1-one (**9f**)²²

Prepared from acylcyanohydrin **8f** and EtMgBr. Purification by flash chromatography on silica gel (20% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9f** (95 mg, 68%) as orange crystals; mp = 51–53 °C (lit: 56–58 °C). IR (neat): $\tilde{\nu}$ = 3253, 2959, 2929, 2869, 1698, 1655, 1398, 1227, 1119, 966 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 6.19 (bs, 1H), 2.44–2.37 (m, 6H), 1.58 (app sx, J = 7.5 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 203.5, 149.0, 148.4, 32.0, 30.8, 25.3, 20.3, 14.2. HRMS (CI- CH_4/NH_3): calcd. for $\text{C}_8\text{H}_{13}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 141.0916; found 141.0914.

4.2.7. 2-Hydroxy-3-isobutylcyclopent-2-en-1-one (**9g**)

Prepared from acylcyanohydrin **8g** and EtMgBr. Purification by flash chromatography on silica gel (20% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9g** (97 mg, 63%) as a beige solid; mp = 78–80 °C. IR (neat): $\tilde{\nu}$ = 3260, 2955, 2921, 1704, 1659, 1410, 1238, 1108, 978 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 6.04 (bs, 1H), 2.45–2.39 (m, 4H), 2.29 (d, J = 7.4 Hz, 2H), 1.97 (app non, J = 6.6 Hz, 1H), 0.94 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 203.4, 149.5, 147.6, 38.1, 32.0, 27.1, 25.8, 22.9. HRMS (EI): calcd. for $\text{C}_9\text{H}_{14}\text{O}_2$ [M^+] 154.0994; found 154.0996.

4.2.8. 3-(Dec-9-en-1-yl)-2-hydroxycyclopent-2-en-1-one (**9h**)

Prepared from acylcyanohydrin **8h** and EtMgBr. Purification by flash chromatography on silica gel (20% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9h** (163 mg, 69%) as a beige solid; mp = 164–166 °C. IR (neat) $\tilde{\nu}$ = 3227, 2925, 2854, 1707, 1640, 1395, 1115 cm^{-1} . ^1H NMR (400 MHz,

CDCl_3): δ (ppm) 6.38 (bs, 1H), 5.85–5.75 (m, 1H), 5.02–4.88 (m, 2H), 2.47–2.38 (m, 3H), 2.34 (t, J = 7.5 Hz, 1H), 2.08–1.98 (m, 2H), 1.68–1.50 (m, 2H), 1.40–1.25 (m, 12H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 203.9, 179.2, 148.9, 139.3, 114.3, 33.9, 32.0, 29.7, 29.4, 29.2, 29.0, 28.8, 27.0, 25.4, 24.8. HRMS (EI): calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_2$ [M^+] 236.1776; found 236.1774.

4.2.9. 2-Hydroxy-3-(phenylethynyl)cyclopent-2-en-1-one (**9i**)²³

Prepared from acylcyanohydrin **8i** and EtMgBr. Purification by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9i** (42 mg, 21%) as a colorless oil. ^1H NMR (200 MHz, CDCl_3): δ (ppm) 7.54 (m, 2H), 7.38–7.35 (m, 3H), 6.0 (bs, 1H), 2.73–2.68 (m, 2H), 2.55–2.50 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 202.2, 154.0, 132.0, 129.4, 128.6, 122.9, 122.5, 104.9, 83.2, 31.8, 26.0.

4.2.10. 4-Ethyl-2-hydroxy-3-phenylcyclopent-2-en-1-one (**9j**)

Prepared from acylcyanohydrin **8a** and BuMgBr. Purification by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9j** (89 mg, 44%) as a beige solid; mp = 116–118 °C. IR (neat): $\tilde{\nu}$ = 3280, 3062, 3021, 2953, 2871, 1738, 1683, 1495, 1455, 1386, 1298, 1113 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.81 (m, 2H), 7.45 (m, 2H), 7.36 (m, 1H), 6.42 (s, 1H), 3.30 (dddd, J = 9.0, 6.3, 2.9, 1.2 Hz, 1H), 2.71 (dd, J = 19.2, 6.3 Hz, 1H), 2.27 (dd, J = 19.2, 1.2 Hz, 1H), 1.90 (m, 1H), 1.33 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (50 MHz, CDCl_3): δ (ppm) 202.9, 148.3, 143.0, 133.1, 129.2, 128.7, 128.4, 37.7, 36.5, 27.3, 10.8. HRMS (CI- CH_4/NH_3): calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 203.1072; found 203.1084.

4.2.11. 4-Benzyl-2-hydroxy-3-phenylcyclopent-2-en-1-one (**9k**)

Prepared from acylcyanohydrin **8a** and $\text{Ph}(\text{CH}_2)_3\text{MgBr}$. Purification by flash chromatography on silica gel (5% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9k** (79 mg, 30%) as a beige solid; mp = 147–149 °C. IR (neat): $\tilde{\nu}$ = 3295, 2918, 1675, 1623, 1493, 1449, 1386, 1294, 1130, 1029 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.93 (m, 2H), 7.49 (m, 2H), 7.39 (m, 1H), 7.27 (m, 2H), 7.21 (m, 1H), 7.13 (m, 2H), 6.88 (s, 1H), 3.65 (m, 1H), 3.24 (dd, J = 14.1, 3.3 Hz, 1H), 2.55 (dd, J = 19.3, 6.1 Hz, 1H), 2.40 (dd, J = 14.1, 9.9 Hz, 1H), 2.34 (d, J = 19.3 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 202.4, 148.7, 142.3, 139.1, 132.9, 129.4, 129.0, 128.9, 128.6, 128.4, 126.6, 40.9, 37.5, 36.7. HRMS (EI): calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_2$ [M^+] 264.1150; found 264.1159.

4.2.12. 4-Allyl-2-hydroxy-3-phenylcyclopent-2-en-1-one (**9l**)

Prepared from acylcyanohydrin **8a** and $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_3\text{MgBr}$. Purification by flash chromatography on silica gel (5% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9l** (75 mg, 35%) as a white solid; mp = 106–108 °C. IR (neat): $\tilde{\nu}$ = 3267, 2931, 2912, 1681, 1638, 1443, 1382, 1118 cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ (ppm) 7.84 (m, 2H), 7.52–7.32 (m, 3H), 6.78 (s, 1H), 5.71 (m, 1H), 5.09–4.98 (m, 2H), 3.45 (m, 1H), 2.69 (dd, J = 19.3, 6.1 Hz, 1H), 2.59 (m, 1H), 2.34 (dd, J = 19.3, 1.2 Hz, 1H), 2.07 (m, 1H). ^{13}C NMR (50 MHz, CDCl_3): δ (ppm) 202.5, 148.5, 142.1, 134.7, 132.8, 129.3, 128.8, 128.3, 117.8, 38.6, 37.5, 34.6. HRMS (EI): calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_2$ [M^+] 214.0994; found 214.1004.

4.2.13. 4-Allyl-2-hydroxy-3-(4-((trimethylsilyl)ethynyl)phenyl)cyclopent-2-en-1-one (**9m**)

Prepared from acylcyanohydrin **8m** and $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_3\text{MgBr}$. Purification by flash chromatography on silica gel (5% ethyl acetate/cyclohexane) provided the pure cyclopentenone **9m** (81 mg, 34%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3301, 3238, 2955, 2925, 2854, 2106, 1681, 1629, 1447, 1391, 1305, 1275, 1120 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.79 (m, 2H), 7.57 (m, 2H), 6.64 (s, 1H), 5.68 (ddt, J = 17.2, 10.3, 6.9 Hz, 1H), 5.09–4.99 (m, 2H), 3.42 (m, 1H), 3.18 (s, 1H), 2.68 (dd, J = 19.3, 6.3 Hz, 1H), 2.56 (m, 1H), 2.34 (dd, J = 19.3, 1.2 Hz, 1H), 2.05 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 202.2, 148.8, 140.5, 134.5, 133.2, 132.5, 128.2, 122.8, 118.0, 83.6, 78.9, 38.5, 37.5, 34.5. HRMS (EI): calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_2$ [M^+] 238.0994; found 238.0990.

4.3. 5-Oxo-2-phenyl-cyclopent-1-en-1-yl-trifluoromethane sulfonate (**12**)

To a solution of triflic anhydride (0.18 mL, 1.1 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C under argon, was slowly added a solution of cyclopentenone **9a** (174 mg, 1 mmol) and pyridine (0.16 mL, 2 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at 0 °C for 2 h then water (10 mL) was added. The phases were separated and the aqueous fraction was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with water (2 × 25 mL), dried over MgSO_4 and filtered. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (15% ethyl acetate/cyclohexane) to afford triflate **12** (257 mg, 84%) as a beige solid; mp = 87–89 °C. IR (neat): $\tilde{\nu}$ = 1722, 1633, 1424, 1410, 1227, 1205, 1134, 1041 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.73 (m, 2H), 7.55–7.48 (m, 3H), 3.12–3.08 (m, 2H), 2.67–2.62 (m, 2H). ^{19}F NMR (375 MHz, CDCl_3): δ (ppm) -73.52 (s, 3F). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 197.1, 158.5, 143.0, 132.1, 129.2, 127.9, 120.0, 116.8, 31.3, 25.5. HRMS (ESI): calcd. for $\text{C}_{12}\text{H}_{10}\text{F}_3\text{O}_4\text{S}$ [$\text{M} + \text{H}$]⁺ 307.0246; found 307.0242.

4.4. (E)-3-Phenyl-2-(phenylethenyl)cyclopent-2-en-1-one (**13**)

To a solution of triflate **12** (53 mg, 0.17 mmol) in DMF (3.4 mL) under argon were successively added freshly distilled triethylamine (23 μL , 0.17 mmol), $\text{Pd}(\text{OAc})_2$ (1.6 mg, 6.9 μmol , 4 mol%), triphenylphosphine (0.9 mg, 3.5 μmol , 2 mol%) and styrene (20 μL , 0.17 mmol). The mixture was stirred at 70 °C for 16 h then water (5 mL) was added. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with brine (3 × 5 mL), dried over MgSO_4 and filtered. After concentration under reduced pressure, the residue was purified by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) to afford the styrenyl-derivative **13** (36 mg, 81%) as an orange oil. IR (neat): $\tilde{\nu}$ = 2925, 2363, 1700, 1588, 1447, 1365, 1074 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.88 (d, J = 16.2 Hz, 1H), 7.53–7.42 (m, 7H), 7.33–7.26 (m, 2H), 7.25–7.19 (m, 1H), 6.89 (dt, J = 16.2, 0.9 Hz, 1H), 2.97–2.92 (m, 2H), 2.65–2.60 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 207.9, 168.6, 137.8, 136.6, 134.6, 133.9, 129.8, 128.8, 128.7, 128.6, 128.1, 127.9, 126.8, 118.4, 35.5, 29.6. HRMS (EI): calcd. for $\text{C}_{19}\text{H}_{16}\text{O}$ [M^+] 260.1201; found 260.1193.

4.5. 3-Phenyl-2-((trimethylsilyl)ethynyl)cyclopent-2-en-1-one (**14**)

To a solution of triflate **12** (153 mg, 0.5 mmol) in THF (10 mL) under argon were successively added $\text{PdCl}_2(\text{PPh}_3)_2$ (18 mg, 0.025 mmol, 5 mol%), CuI (9.5 mg, 0.05 mmol, 10 mol%), freshly distilled $i\text{Pr}_2\text{NEt}$ (85 μL , 0.5 mmol) and trimethylsilylacetylene (80 μL , 0.55 mmol). The mixture was stirred overnight at 53 °C then cooled down to room temperature. After filtration through a pad of Celite® and evaporation of the solvents under reduced pressure, the crude residue was purified by flash chromatography on silica gel (10% ethyl acetate/cyclohexane) to afford the alkynyl-derivative **14** (120 mg, 94%) as a white solid; mp = 201–203 °C. IR (neat): $\tilde{\nu}$ = 3569, 2925, 1707, 1603, 1261, 1235, 1175, 1037 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.16 (m, 2H), 7.53–7.41 (m, 3H), 3.06 (ddd, J = 5.2, 2.6, 2.6 Hz, 2H), 2.58 (ddd, J = 5.2, 2.6, 2.6 Hz, 2H), 0.27 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 205.6, 171.9, 134.5, 131.6, 128.6, 127.9, 122.9, 106.6, 97.7, 34.2, 28.5, -0.2. HRMS (CI- CH_4/NH_3): calcd. for $\text{C}_{16}\text{H}_{19}\text{OSi}$ [$\text{M} + \text{H}$]⁺ 255.1205; found 255.1214.

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17. Some degradation of the diketones **11** may occur during the purification process. For instance, the diketone **11a** was estimated to be formed in 86% yield in the crude NMR, but it was isolated in only 69% yield after column chromatography.
18. All attempts to couple triflate **12** with ethyl acrylate using different solvents (DMF, THF) and conditions (Pd(PPh₃)₄, Pd(OAc)₂, triethylamine, ethyldiisopropylamine, ...) failed.
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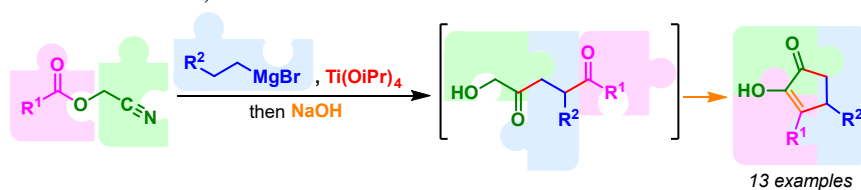
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