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Selective Acceptorless Dehydrogenation and Hydrogenation by Iridium Catalysts Enabling Facile Interconversion of Glucocorticoids

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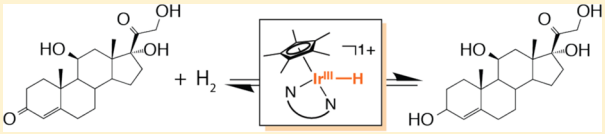
Supporting Information

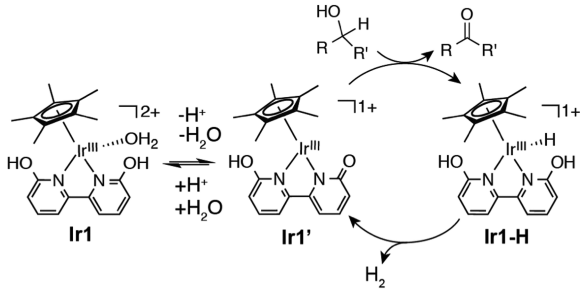
ABSTRACT: An iridium(III) pentamethylcyclopentadienyl catalyst supported by 6,6′-dihydroxy-2,2′-bipyridine displays exquisite selectivity in acceptorless alcohol dehydrogenation of cyclic α,β-unsaturated alcohols over benzylic and aliphatic alcohols under mild aqueous reaction conditions. Hydrogenation of aldehydes and ketones occurs indiscriminately using the same catalyst under hydrogen, although chemoselectivity could be achieved when other potentially reactive carbonyl groups present are sterically inaccessible. This chemistry was demonstrated in the reversible hydrogenation and dehydrogenation of the A ring of glucocorticoids, despite the presence of other alcohol/or carbonyl functionalities in rings C and D. NMR studies suggest that an iridium(III) hydride species is a key intermediate in both hydrogenation and dehydrogenation processes.



Transition-metal hydrides are key reaction intermediates in numerous catalytic organometallic transformations. The formation of such species allows the efficient shuttling of nucleophilic hydrides derived from primary and secondary alcohols to electrophilic carbonyl groups (transfer hydrogenation) or to protons to generate hydrogen gas (acceptorless dehydrogenation).[1,2] A variety of hydrogenation/dehydrogenation systems based on metal ions such as Ru,[3−6] Rh,[7,8] Ir,[9,10] Fe,[11−16] and Co[17] have been reported, which have demonstrated practical utility ranging from enantioselective chemical synthesis[5] to facile hydrogen release from liquid fuels.[18−20]

In our program to develop atom-economical methods to elaborate complex biomolecules, we were intrigued by alcohol dehydrogenation catalysts that require neither sacrificial hydride acceptors nor base additives (Scheme 1).[2] During the course of our studies we discovered an iridium(III) pentamethylcyclopentadienyl (Cp*) complex[21−26] that is unreactive toward benzylic/aliphatic alcohols but reactive toward allylic alcohols. Such chemoselectivity is rare and, to the best of our knowledge, has only been achieved using catalyst systems that employ external oxidants.[27,28] We describe herein the unusual dehydrogenation and hydrogenation chemistry of an organometallic iridium catalyst and demonstrate its utility in the selective interconversion of glucocorticoids,[29] an important class of naturally occurring steroids.

Scheme 1. Proposed Mechanism for Alcohol Dehydrogenation by Ir1



Recently, it was reported that [Cp*Ir(6,6′-dihydroxy-2,2′-bipyridine)(H_2O)]$^{2+}$ (**Ir1**; Scheme 1)[23] bearing a functional bipyridine ligand efficiently converts benzylic and secondary alcohols to aldehydes and ketones, respectively, in aqueous media. Under the conditions tested in our laboratory (Table S1, Supporting Information), including in aqueous buffers at different pH values, we did not observe reactivity with benzylic (entries 1−4, Table 1) or saturated aliphatic alcohols (entries 5−7). When we expanded the scope of our substrate studies, we discovered that cyclic α,β-unsaturated alcohols were dehydrogenatively oxidized to their corresponding enones using 2 mol % of **Ir1** in air in *tert*-butyl alcohol/water (1/9), with yields ranging from modest to excellent (entries 8−11). For compounds containing six-membered rings, reversible isomerization of the starting substrate was observed (Schemes S1 and S2, Supporting Information).[30−32] However, dehydrogenation to the enone is favored in the absence of added hydrogen; in fact, a nearly quantitative yield of 3-methylcyclohex-2-en-1-one was obtained from reaction of **Ir1** with 3-methylcyclohex-2-en-1-ol after 24 h (entry 9). Dehydrogenation of the seven-membered ring cyclohept-2-en-1-ol proceeded slowly, as indicated by its low conversion and yield (entry 11). The five-membered-ring 3-methylcyclopent-2-en-1-ol was fully consumed after 24 h, but no 3-methylcyclopent-2-en-1-one was detected by GC (entry 12); instead, this reaction afforded significant amounts of an intractable solid.

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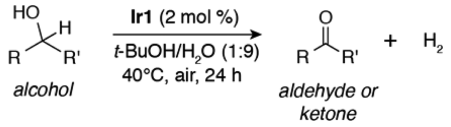
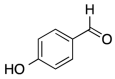
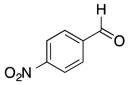
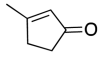
Table 1. Alcohol Dehydrogenation Study[a]



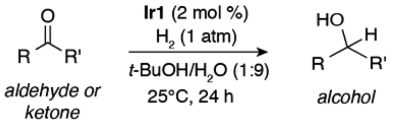
Entry	Product	Conversion,%[b,c]	Yield,%[c]
1		0	0
2		0	0
3		0	0
4		0	0
5		0	0
6		0	0
7		0	0
8		64	40[d]
9		99	92
10		63	35[d]
11		17	12
12		99	0[e]
13		13[f]	13[f]
14		9[f]	9[f]

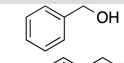
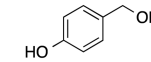
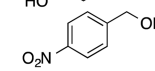
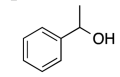
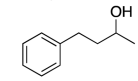
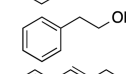
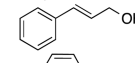
[a]Conditions: alcohol (0.50 mmol), **Ir1** catalyst (10 μmol), *t*-BuOH/H_2O (1/9, 1.0 mL), sealed reaction vial in air. [b]Conversion defined as: 100% − [(starting material)/(starting material + product)] × 100%. [c]Determined by GC relative to internal standard. Averaged from duplicate runs. [d]Addtional side products were obtained. See Schemes S1 and S2 (Supporting Information). [e]An intractable solid was isolated. [f]Determined by NMR spectroscopy.

Surprisingly, linear allylic alcohols were found to react poorly in the presence of **Ir1** at 40 °C (entries 13 and 14), with yields only up to ∼13% of the corresponding enone, as quantified by ^{1}H NMR spectroscopy and gas chromatography. Acyclic enones have been shown to form strong s-cis adducts to transition-metal complexes,[33,34] which may result in catalyst inhibition by blocking substrate coordination sites at the metal center. In contrast, cyclic enones have s-trans geometric configurations and thus, cannot bind to transition metal ions as tightly as in the s-cis form. Nevertheless, the unusual reactivity of **Ir1** toward *cyclic* allylic alcohols over a variety of other alcohols makes it an unusually chemoselective oxidation catalyst.

Next, we explored whether hydrogenation of aldehydes and ketones by **Ir1** was possible. Table 2 summarizes the substrates

Table 2. Aldehyde/Ketone Hydrogenation Study[a]



Entry	Product	Yield,%[c]
1		98
2[b]		70[d]
3[b]		99 (89[e])
4		99
5		15
6		94
7		70
8[b]		71

[a]Conditions: aldehyde or ketone (0.50 mmol), **Ir1** catalyst (10 μmol), H_2 (1 atm), *t*-BuOH/H_2O (1/9, 3.0 mL). [b]To improve substrate solubility, *t*-BuOH/H_2O (2/8) was used as solvent. [c]Yields were determined by GC relative to internal standard. Averaged from duplicate runs. [d]Yield determined by NMR. [e]Isolated yield.

that were tested. The reactions were performed using 2 mol % of **Ir1** in *tert*-butyl alcohol/water (1/9) at 25 °C under 1 atm of hydrogen gas. No special precautions were taken to exclude air from the reaction vials. Under optimized reaction conditions, hydrogenation of a variety of carbonyl-containing compounds was achieved, including benzaldehydes (entries 1−3), acetophenone (entry 4), aliphatic ketones (entry 5)/aldehydes (entry 6), and enones (entries 7−8). As expected, substrates with electron-withdrawing groups were reduced more efficiently than those with electron-donating groups, showing the trend 4-nitrobenzaldehyde ≈ benzaldehyde > 4-hydroxybenzaldehyde, suggesting that hydride transfer is the rate-determining step in the reaction.[35] Complete hydrogenation of cinnamyl alcohol to 3-phenylpropanol (entry 7) was not observed, whereas a small amount of cyclohexanol was obtained from hydrogenation of cyclohex-2-en-1-one using **Ir1**/H_2, which presumably formed through a sequential isomerization and hydrogenation mechanism (Scheme S1, Supporting Information) rather than by direct reduction of the C=C double bond.

To gain greater insight into the reactivity of **Ir1**, further mechanistic studies were performed. It is proposed that acceptorless dehydrogenation proceeds by first dehydrogenation of a 1° or 2° alcohol to give the metal hydride species **Ir1-H** and the corresponding aldehyde or ketone, followed by catalyst regeneration via protonation of **Ir1-H** to give H_2 as a byproduct (Scheme 1).[23] The detailed mechanism by which this process occurs has been suggested to involve metal−ligand bifunctional catalysis, in which the 6,6′-dihydroxy-2,2′-bipyridine ligand plays a pivotal role in facilitating proton exchange during catalysis.[36,37] Presumably, in the reverse process (i.e., hydrogenation), the catalyst first heterolytically cleaves H_2 to yield a metal hydride and then transfers the resulting hydride to a carbonyl acceptor. To provide evidence for the formation of

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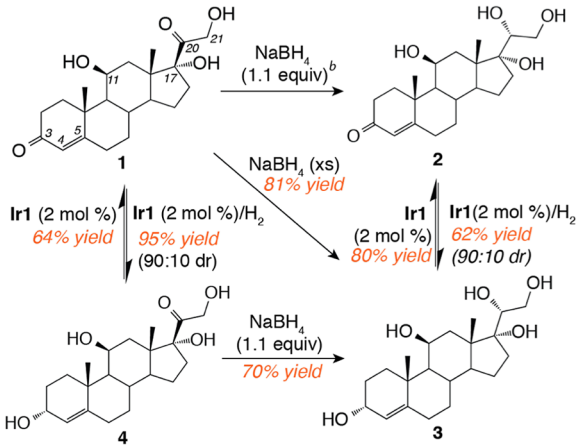
Ir1-H during catalysis, a 1.5 M solution of **Ir1** in D_2O was treated with 15 equiv of 3-methylcyclohex-2-en-1-ol and heated for 2 min at 90 °C. Upon heating, the yellow solution rapidly turned orange ($\lambda_{shoulder}$ ~450 nm). The in situ ^1H NMR spectrum of this mixture showed a peak at −17.74 ppm, which is characteristic of an iridium hydride species.[38] This signal was *not* observed in the absence of cyclohexenol or when benzyl alcohol was used as the hydride donor. The latter is consistent with our observation that **Ir1** does not react with benzylic alcohols (entries 1−4, Table 1). Formation of **Ir1-H** was also clearly seen upon stirring **Ir1** under 100 psi of H_2 in D_2O for 5 min. The ^1H NMR signals at 6.83, 7.44, and 7.74 ppm are attributed to the 6,6′-dihydroxy-2,2′-bipyridine ligand, whereas the signal at 1.42 ppm is assigned to the Cp* ring of **Ir1-H**. Because **Ir1-H** was observed under both dehydrogenation and hydrogenation conditions, it is likely a key reaction intermediate during catalysis. Further support of the acceptorless dehydrogenation mechanism shown in Scheme 1 was obtained from gas chromatographic detection of H_2 in the reaction of **Ir1** with 3-methylcyclohex-2-en-1-ol.

As discussed above, the chemoselectivity of the **Ir1** catalyst is unusual. To demonstrate its utility in chemical synthesis, we explored the application of **Ir1** in the derivatization of cortisol (**1**; Scheme 2), a naturally occurring glucocorticoid that is

Scheme 2. Interconversion of Cortisol and Related Compounds[a]



[a]Percent yields shown are isolated yields. [b]Compound **2** could not be separated from **3**.

essential to many physiological functions. This compound is an ideal model substrate because it has several potentially reactive alcohol and carbonyl groups, including a cyclic enone in the A ring of the steroid structure. Upon treatment of **1** with 1.1 equiv of sodium borohydride,[39,40] the more electrophilic C20 carbonyl moiety was reduced first to afford 11*β*,17*α*,20*R*,21-tetrahydroxypregn-4-en-3-one (**2**),[41] with a minor amount of the doubly reduced compound 3,11*β*,17*α*,20*R*,21-pentahydroxypregn-4-ene (**3**). To obtain **3** in high yield, **1** was treated with excess sodium borohydride. Interestingly, $NaBH_4$ reduction of **1** at C20 gives predominantly the 20*R*-OH stereocenter,[42] whereas reduction at C3 affords 3*α*-OH (**3a**)/3*β*-OH (**3b**)[29,43,44] in an 83/17 ratio.[45] When **3** was stirred in the presence of 2 mol % of **Ir1** in *tert*-butyl alcohol/water (1/9) at 60 °C for 11 h, dehydrogenation of the C3 alcohol occurred preferentially over other primary and secondary alcohol groups in rings C and D. Compound **2** was isolated in ~80% yield. The conversion of **3** to **2** was readily followed by ^1H NMR spectroscopy,[41,46] as indicated by the disappearance of the H3 peak at 4.05 ppm and downfield shift of H4 from 5.16 to 5.64 ppm (Figure 1; compare the spectrum of **3** vs that of **2**).

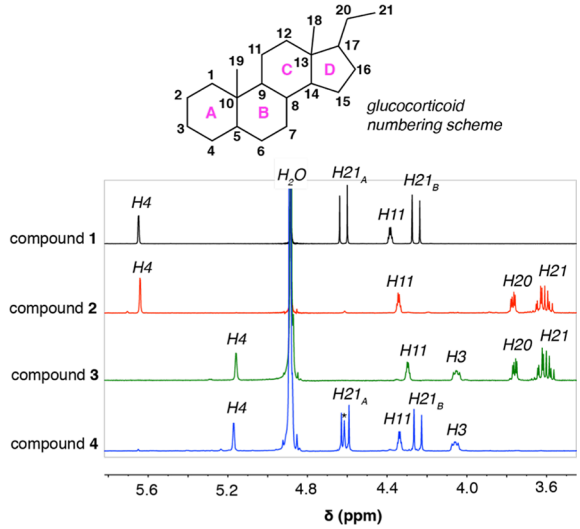


Figure 1. ^1H NMR spectra of glucocorticoids **1**−**4** (CD_3OD, 500 MHz). The signal marked with an asterisk is derived from an impurity in the preparative TLC plate used during purification.

Although our substrate studies above (Table 2) indicate that hydrogenation of aldehydes/ketones using **Ir1** is not chemoselective, further investigations revealed that chemoselectivity could be achieved in certain cases. When cortisol **1** was stirred under 100 psi of H_2 and 2 mol % of **Ir1** at room temperature for 24 h, the ^1H NMR spectrum of the product (95% yield) showed an upfield shift of H4 from 5.65 to 5.17 ppm and the appearance of H3 at 4.06 ppm (Figure 1, compare the spectrum of **4** vs that of **1**). The doublets at 4.25 and 4.61 ppm appear at the same chemical shifts as those of the C21 methylene protons in **1**, indicating that the C20 carbonyl *was not* reduced. The NMR data strongly suggest that **1** was selectively hydrogenated to 3,11*β*,17*α*,21-tetrahydroxypregn-4-en-20-one (**4**), which was obtained as a diastereomeric mixture of 3*α*-OH (**4a**)/3*β*-OH (**4b**) in a 90/10 ratio. The assignment of stereochemistry at C3 in **4** was based on similarities of its chemical shifts to those of **3a** and **3b**.[47] To support the identity of **4**, reaction of **4** with 1.1 equiv of $NaBH_4$ gave the expected compound **3** in ~70% isolated yield (Scheme 2). Confirmation of the identity of **4** was obtained from high-resolution electrospray ionization mass spectral analysis, which shows *m*/*z* 387 corresponding to $[M + Na]^+$. Finally, hydrogenation at the C3 position of **2** to **3** using 2 mol % of **Ir1** and H_2 was also achieved successfully.

Although chemoselective methods to hydrogenate steroids have been reported,[29,40] they are often prone to give side products. For example, hydroboration of progesterone affords predominately the C3 alkenol product but also minor amounts of the C=C double bond and C20 carbonyl reduced species.[48] In contrast, the conversion of **1** to **4** using **Ir1** yields a single enone product under mild reaction conditions.

In summary, we have identified an air- and water-compatible iridium(III) catalyst that is efficient at both oxidation of cyclic allylic alcohols *and* reduction of aldehydes and ketones under the appropriate reaction conditions. Spectroscopic studies provide evidence for the formation of an iridium hydride

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intermediate during catalysis, and detection of H_2 as a reaction byproduct supports an acceptorless alcohol dehydrogenation mechanism. This chemistry allows easy access to several glucocorticoid derivatives, which may be useful in studies of steroid metabolism[29,41] or as possible chemotherapeutics[43,44,49] and drug conjugates.[50−52] Future investigations will explore the underlying reasons for chemoselectivity as well as the generality of this behavior in related catalyst systems.

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental procedures and physical methods, GC plots, schemes, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.
(2) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712.
(3) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285.
(4) Dobson, A.; Robinson, S. D. *Inorg. Chem.* **1977**, *16*, 137.
(5) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.
(6) Nielsen, M.; Kammer, A.; Cozzula, D.; Junge, H.; Gladiali, S.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9593.
(7) Brewster, T. P.; Miller, A. J. M.; Heinekey, D. M.; Goldberg, K. I. *J. Am. Chem. Soc.* **2013**, *135*, 16022.
(8) Blacker, A. J.; Clot, E.; Duckett, S. B.; Eisenstein, O.; Grace, J.; Nova, A.; Perutz, R. N.; Taylor, D. J.; Whitwood, A. C. *Chem. Commun.* **2009**, 6801.
(9) Tang, W.; Johnston, S.; Iggo, J. A.; Berry, N. G.; Phelan, M.; Lian, L.; Bacsa, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1668.
(10) Royer, A. M.; Rauchfuss, T. B.; Gray, D. L. *Organometallics* **2010**, *29*, 6763.
(11) Song, H.; Kang, B.; Hong, S. H. *ACS Catal.* **2014**, *4*, 2889.
(12) Bielinski, E. A.; Lagaditis, P. O.; Zhang, Y.; Mercado, B. Q.; Würtele, C.; Bernskoetter, W. H.; Hazari, N.; Schneider, S. *J. Am. Chem. Soc.* **2014**, *136*, 10234.
(13) Zell, T.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 4685.
(14) Moyer, S. A.; Funk, T. W. *Tetrahedron Lett.* **2010**, *51*, 5430.
(15) Quintard, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4044.
(16) Chakraborty, S.; Brennessel, W. W.; Jones, W. J. *J. Am. Chem. Soc.* **2014**, *136*, 8564.
(17) Zhang, G.; Vasudevan, K. V.; Scott, B. L.; Hanson, S. K. *J. Am. Chem. Soc.* **2013**, *135*, 8668.
(18) Johnson, T. C.; Morris, D. J.; Wills, M. *Chem. Soc. Rev.* **2010**, *39*, 81.
(19) Nielson, M.; Alberico, E.; Baumann, W.; Drexler, H.-J.; Junge, H.; Gladiali, S.; Beller, M. *Nature* **2013**, *495*, 85.
(20) Brewster, T. P.; Ou, W. C.; Tran, J. C.; Goldberg, K. I.; Hanson, S. K.; Cundari, T. R.; Heinekey, D. M. *ACS Catal.* **2014**, *4*, 3034.
(21) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 12790.
(22) Fujita, K.-i.; Tanaka, Y.; Kobayashi, M.; Yamaguchi, R. *J. Am. Chem. Soc.* **2014**, *136*, 4829.
(23) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *J. Am. Chem. Soc.* **2012**, *134*, 3643.
(24) Zeng, G.; Sakaki, S.; Fujita, K.-i.; Sano, H.; Yamaguchi, R. *ACS Catal.* **2014**, *4*, 1010.
(25) Fujita, K.-i.; Ito, W.; Yamaguchi, R. *ChemCatChem* **2014**, *6*, 109.
(26) DePasquale, J.; Nieto, I.; Reuther, L. E.; Herbst-Gervasoni, C. J.; Paul, J. J.; Mochalin, V.; Zeller, M.; Thomas, C. M.; Addison, A. W.; Papish, E. T. *Inorg. Chem.* **2013**, *52*, 9175.
(27) Shen, S.-S.; Kartika, V.; Tan, Y. S.; Webster, R. D.; Narasaka, K. *Tetrahedron Lett.* **2012**, *53*, 986.
(28) Cosner, C. C.; Cabrera, P. J.; Byrd, K. M.; Thomas, A. M. A.; Helquist, P. *Org. Lett.* **2011**, *13*, 2071.
(29) Okihara, R.; Mitamura, K.; Hasegawa, M.; Mori, M.; Muto, A.; Kakiyama, G.; Ogawa, S.; Iida, T.; Shimada, M.; Mano, N.; Ikegawa, S. *Chem. Pharm. Bull.* **2010**, *58*, 344.
(30) Mantilli, L.; Mazet, C. *Tetrahedron Lett.* **2009**, *50*, 4141.
(31) Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745.
(32) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Varela-Álvarez, A.; Sordo, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 1360.
(33) Kanaya, S.; Imai, Y.; Komine, N.; Hirano, M.; Komiya, S. *Organometallics* **2005**, *24*, 1059.
(34) Daugulis, O.; Brookhart, M. *Organometallics* **2004**, *23*, 527.
(35) DePasquale, J.; Kumar, M.; Zeller, M.; Papish, E. T. *Organometallics* **2013**, *32*, 966.
(36) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466.
(37) Wang, W.-H.; Hull, J. F.; Muckerman, J. T.; Fujita, E.; Himeda, Y. *Energy Environ. Sci.* **2012**, *5*, 7923.
(38) Fujita, K.-i.; Yoshida, T.; Imori, Y.; Yamaguchi, R. *Org. Lett.* **2011**, *13*, 2278.
(39) Ward, D. E.; Rhee, C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517.
(40) Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23.
(41) Yazdi, M. T.; Arabi, H.; Faramarzi, M. A.; Ghasemi, Y.; Amini, M.; Shokravi, S.; Mohseni, F. A. *Phytochemistry* **2004**, *65*, 2205.
(42) Gardi, R.; Vitali, R.; Ercoli, A.; Klyne, W. *Tetrahedron* **1965**, *21*, 179.
(43) Pokhrel, M.; Ma, E. *Molecules* **2011**, *16*, 9868.
(44) Varela, C.; Tavares da Silva, E. J.; Amaral, C.; Correia da Silva, G.; Baptista, T.; Alcaro, S.; Costa, G.; Carvalho, R. A.; Teixeira, N. A. A.; Roleira, F. M. F. *J. Med. Chem.* **2012**, *55*, 3992.
(45) The 3α-OH epimer has been reported to be the major isomer obtained from sodium borohydride reduction of enones in cortisol-type steroidal compounds. The chemical shift of the H3 proton is more downshifted in 3α-OH in comparison to that in the 3β-OH epimer.
(46) Kirk, D. N.; Toms, H. C.; Douglas, C.; White, K. A.; Smith, K. E.; Latif, S.; Hubbard, R. W. P. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1567.
(47) The H3 signals in the proton NMR spectra of the 3α-OH and 3β-OH epimers of compound **4** appear at 4.06 and 4.01 ppm, respectively.
(48) Stefanović, M.; Lajšić, S. *Tetrahedron Lett.* **1967**, *19*, 1777.
(49) Bansal, R.; Acharya, P. C. *Chem. Rev.* **2014**, *114*, 6986.
(50) Huxley, M.; Sanchez-Cano, C.; Browning, M. J.; Navarro-Ranninger, C.; Quiroga, A. G.; Rodger, A.; Hannon, M. J. *Dalton Trans.* **2010**, *39*, 11353.
(51) Sanchez-Cano, C.; Huxley, M.; Ducani, C.; Hamad, A. E.; Browning, M. J.; Navarro-Ranninger, C.; Quiroga, A. G.; Rodger, A.; Hannon, M. J. *Dalton Trans.* **2010**, *39*, 11365.
(52) Levine, P. M.; Garabedian, M. J.; Kirshenbaum, K. *J. Med. Chem.* **2014**, *57*, 8224.