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Electrophilic monoiodination of terminal alkenes†

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An excess of elemental iodine in *N*,*N*-dimethylacetamide enables effective 3/iodanylium-de-hydronation of terminal alkenes with 3-iodopropene derivatives and hydrogen iodide formation within minutes at room temperature. The optimal molar ratio of iodine to substrate was decreased to 1 : 1 when hydrogen iodide formed was oxidized on a platinum anode. The electrolytic oxidation recovers iodine as a reagent and diminishes the hydrogen iodide inhibitory action to accomplish the monoiodination. The proposed reaction mechanism is based on kinetic measurements and quantum mechanics calculations.

Introduction

The potential of iodine in organic synthesis is described in numerous recent reviews.[1–3] The electrophilic addition of iodine to a double bond particularly is well studied with many useful variations. The activation of certain unsaturated carbons with iodine substituents can be considered as a general concept for synthesis because iodine is an excellent leaving group for various bond formations.

This study is devoted to the development of a new process for terminal carbon activation through electrophilic monoiodination of terminal alkenes. The approach of 3/halogenanylium-de-hydronation is principally different from other terminal alkene monohalogenations – the Wohl–Ziegler reaction[4] – which is a radical substitution process at the allylic and benzylic positions with NBS or NCS and initiators (peroxides, AIBN or UV light). Use of *N*-iodosuccinimide (NIS) and elemental iodine has not been reported in such radical processes because direct radical iodination is highly endothermic and an iodine radical itself is not capable of hydrogen abstraction from C–H bonds.[5–7] These factors provide the limited information about processes of radical iodination of C–H bonds.[8] Iodination of terminal alkenes with I_2 or NIS was used to a lesser extent.[9a–c] Halogenation of 1,1-disubstituted alkenes with NCS, NBS and NIS mediated by $Yb(OTf)_3$–TMSCl suggested that monohalogenation of terminal alkenes proceeded *via* a non-free-radical mechanism.[10] The goal of this work is connected with the use of reactive iodoallylic derivatives for synthesis of a broad range of new and useful organic molecules by reactions of substitution with various nucleophilic reagents.

Results and discussion

The following terminal alkenes were used for this study: betulin (**1**), betulonic aldehyde (**2**), betulinic acid (**3**), 2,3,3-trimethylbut-1-ene (**4**), methylenecyclohexane (**5**), α-methylstyrene (**6**) and 2-(1-adamantyl)propene (**7**) (Table 1, Scheme 1).

The use of elemental iodine in different non-polar (hexane, benzene, CCl_4) and polar solvents (THF, CH_2Cl_2, $CHCl_3$) did not give any good results. NMR analyses of reaction mixtures show, besides starting triterpenes and admixture of iodides, the presence of products of their transformation. The formation of monoiodinated main products (**8–14**) was observed when the reaction was performed in *N*,*N*-dimethylacetamide at room temperature for 1–15 min. Optimization of the iodine to substrate ratio, reaction time and concentration led to the monoiodides (**8–14**) synthesis procedures (Table 1).

It was observed that this monoiodination is not occurring for non-terminal or conjugated alkenes. Lower yield of 2,3,3-trimethylbut-1-ene (**4**) may be explained by a fast consecutive process of DMA *O*-alkylation[11] with the formed monoiodide. Discussion of this reaction is outside the scope of this study. Here we only note that it was necessary to stop the reaction of monoiodination for this substrate at a lower conversion level for better isolation of the monoiodide (**11**). *N*,*N*-Dimethylformamide also could be used as a medium for similar monoiodinations instead of DMA, but more contaminated products resulted due to the much faster DMF *O*-alkylation with the formed monoiodides.

The allylic radical iodination – the Wohl–Ziegler reaction – in such polar solvents and reaction conditions (room temperature) is unlikely and has never been observed. It has been shown (quantum mechanics calculations, kinetic and thermodynamic studies discussed below) that charge transfer

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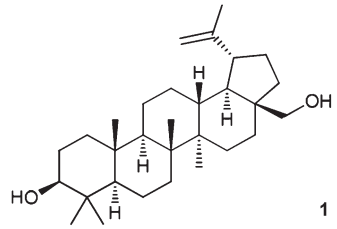
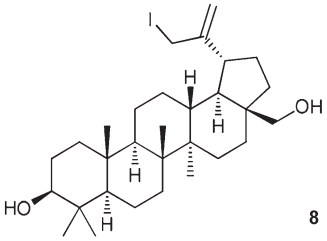
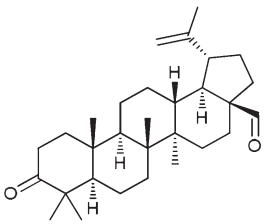
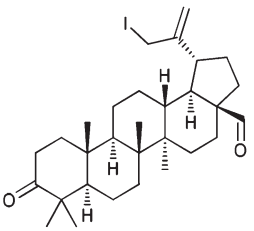
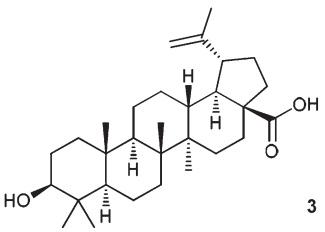
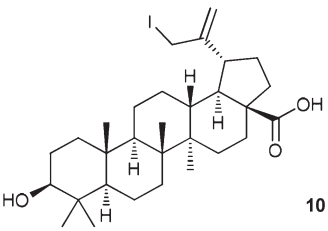
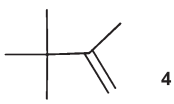
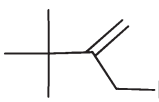
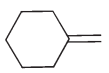
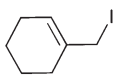
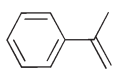
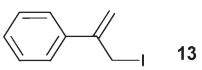
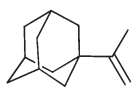
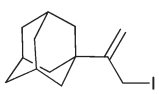
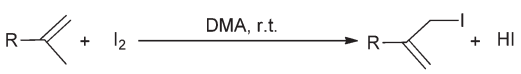
†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra, kinetic measurement data and optimized geometries for all species. See DOI: 10.1039/c3ob27348b

Table 1 Monoiodination of terminal alkenes using molecular iodine in *N*,*N*-dimethylacetamide[a]

Alkene	Product	Yield[b] (%)
 1	 8	94
 2	 9	93
 3	 10	75
 4	 11	25
 5	 12	55
 6	 13	75
 7	 14	43

[a] See Scheme 1 and Experimental for details. [b] Yield of the pure product calculated on starting materials.



Scheme 1 Monoiodination of terminal alkenes.

complex **CTC1**[12,13a–c] (Fig. 1) forms a second charge transfer complex **CTC2** with a terminal alkene substrate. The process of allylic 3/iodanylynium-de-hydronation takes place within this **CTC2** with the formation of monoiodides (**8–14**) and hydrogen iodide *via* transition state **TS** (Fig. 1, Scheme 2).

The total potential energy profile for the 3/iodanylium-de-hydronation of 2,3,3-trimethylbut-1-ene (**4**) with iodine in *N*,*N*-dimethylacetamide is described in Fig. 2. PW91PW91/DZVP calculations show that both complexes **CTC1** and **CTC2** are formed exothermically with ΔE_{CTC1} = −8.1 kcal mol^{-1} and ΔE_{CTC2} = −2.5 kcal mol^{-1}. ωB97XD/DZVP and MP2/DZVP calculations show that **CTC2** is formed exothermically with ΔE_{CTC2} = −6.8 and −6.5 kcal mol^{-1} respectively (Fig. 2). **CTC2** is a precursor for synchronous 3/iodanylium-de-hydronation into three products: *N*,*N*-dimethylacetamide, monoiodide (**11**) and hydrogen iodide (Scheme 2). The computed activation barrier (ΔE_{TS} = 28.2 kcal mol^{-1}, PW91PW91/DZVP, up to 45.1 kcal mol^{-1}, MP2/DZVP) appears high for a room temperature reaction. It is obvious that this activation barrier is sufficiently decreased under the highly polar experimental conditions. Inclusion of a DMF solvent effect[14] significantly lowers this barrier to $\Delta E'_{TS}$ = 12.8 kcal mol^{-1} and increases exothermicity of **CTC1** and **CTC2** formation ($\Delta E'_{CTC1}$ = −10.3 kcal mol^{-1} and $\Delta E'_{CTC2}$ = −3.3 kcal mol^{-1}). The reaction ends with a slightly

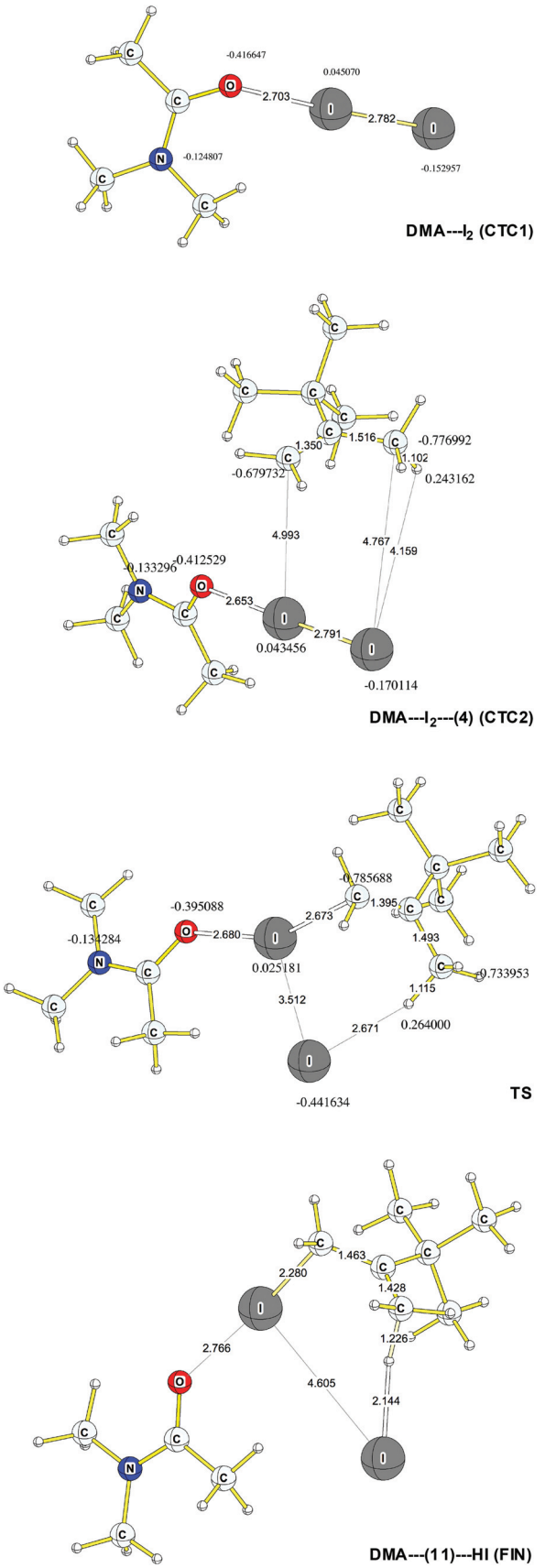


Fig. 1 DFT (PW91PW91/DZVP) computed structures of charge transfer complexes (**CTC1** and **CTC2**), transition state (**TS**) and final cluster (**FIN**).

endothermic (6.9 kcal mol^{-1}, PW91PW91/DZVP or 3.2 kcal mol^{-1}, ωB97XD/DZVP) or exothermic (−1.3 kcal mol^{-1}, MP2/DZVP) formation of the DMA···(**11**)···HI final cluster (**FIN**) (Fig. 1 and 2, Scheme 2). Inclusion of the solvent correction lowers this value to −9.8 kcal mol^{-1}, thus effectively changing the reaction to an exothermic one.

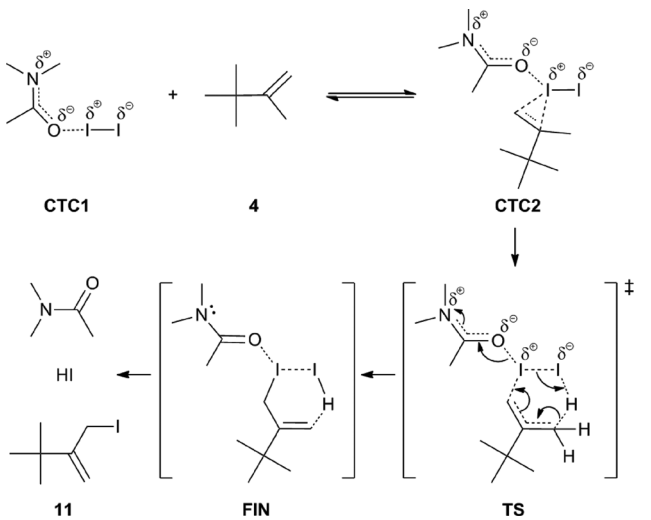
The system of **CTC1** and an alkene substrate was a starting point for experimental kinetic measurements, therefore the determined activation energy E_A can be compared to the theoretical activation energies E_A^T and E'^T_A (Fig. 2). Experimental kinetic measurements were achieved at 25 °C for a betulin (**1**) monoiodination process[15] by ^{1}H NMR monitoring. It is shown that betulin monoiodination in DMA has first order in alkene substrate (**1**) and first order in iodine with the following kinetic equation: $r = k[S][I_2]$, where $k = (3.99 \pm 0.03) \times 10^{-2}$ l mol^{-1} s^{-1}; r is the rate of the reaction, mol l^{-1} s^{-1}; [S] is the concentration of substrate (**1**) and [I_2] is the concentration of iodine, mol l^{-1}. Experimental thermodynamic parameters have been acquired by ^{1}H NMR monitoring of the monoiodination of betulin (**1**) and a kinetic study at 25–65 °C. The following data were obtained: E_A = 6.7 ± 0.4 kcal mol^{-1}, $\Delta H^{\ddagger}_{298}$ = 6.1 ± 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}_{298}$ = −44.6 ± 1.4 cal mol^{-1} K^{-1}, $\Delta G^{\ddagger}_{298}$ = 19.4 ± 0.6 kcal mol^{-1}.

ωB97XD/DZVP and MP2/DZVP calculations gave a higher value of E_A^T (38.3 kcal mol^{-1} and 37.6 kcal mol^{-1}, respectively) than PW91PW91/DZVP (Fig. 2). PW91PW91/DZVP computed E_A^T = 25.7 kcal mol^{-1} decreases to E'^T_A = 9.5 kcal mol^{-1} with inclusion of the DMF solvent model. This theoretical value is comparable with the experimental thermodynamic data for E_A = 6.7 kcal mol^{-1}.

It has been observed that the experimental kinetic parameters are quite stable up to nearly 15% of betulin (**1**) conversion levels. Then the monoiodination process is inhibited sufficiently due to accumulation of hydrogen iodide in the reaction media. It is likely that hydrogen iodide hinders the process of monoiodination by the decomposition of intermediate complexes and binding iodine with the polyiodides formation. The same inhibition effect occurred when potassium iodide was added to the reaction media; no reaction was observed in this case. An excess of iodine was essential to increase the rate of iodination. Iodine should be used with more than two-fold excess to the alkene substrate, otherwise conversion of the substrate and yield of the reaction will be decreased. We have found a way to oxidize hydrogen iodide formed on a platinum anode *in situ* to reduce its inhibiting role. Iodine that is formed returns back to the process of monoiodination. Thus the optimal molar ratio of iodine to alkene was decreased to 1 : 1 (Scheme 3). The presence of urea allows for buffering the reaction media and accelerates the process by three times to obtain a pure product. The fact of acceleration leads to an assumption that urea assists this transformation in a way that DMA does by forming analogous **CTC1** with iodine to interact with alkene. However, the complete conversion of alkene for a 1 : 1 alkene to iodine molar ratio cannot be achieved in the presence of urea alone without use of electrolysis due to the inhibition. The possibility of

chemo-oxidation for transformation of accumulating hydrogen iodide to starting iodine with oxygen was also examined. Oxygen was passed into the reaction mixture of betulin and iodine (1 : 1 molar ratio) in DMA but no significant reduction of the inhibition was observed. The use of the other oxidative reagents does not seem to be favorable because this iodination reaction is very sensitive to the changes in the reaction media. Therefore the use of anodic oxidation seems to be the most appropriate way to neutralize the inhibitory action of hydrogen iodide and to recover iodine in the reaction media.

The principal difference between the studied ionic process and the radical Wohl–Ziegler reaction is described in Scheme 4, when two structurally different products of monohalogenation were formed as a result of electrophilic monoiodination and radical bromination with NBS.[16]



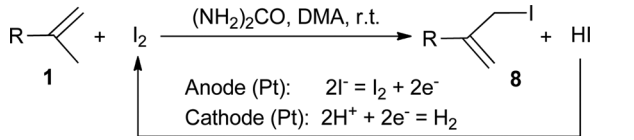
Scheme 2 Plausible reaction pathway for 3/iodanylium-de-hydronation of 2,3,3-trimethylbut-1-ene (**4**).

Conclusion

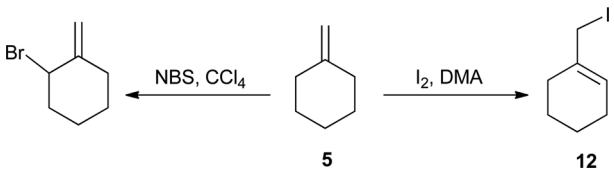
This work demonstrates that a complex of iodine with *N*,*N*-dimethylacetamide is capable of providing fast and low temperature electrophilic monoiodination of terminal alkenes *via* synchronous 3/iodanylium-de-hydronation.

Experimental

NMR spectra (300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR) were recorded using a Varian Unity Inova 300. ^{1}H and ^{13}C NMR



Scheme 3 Electrolysis for monoiodination of betulin (**1**).



Scheme 4 Radical bromination and electrophilic iodination of methylenecyclohexane (**5**).

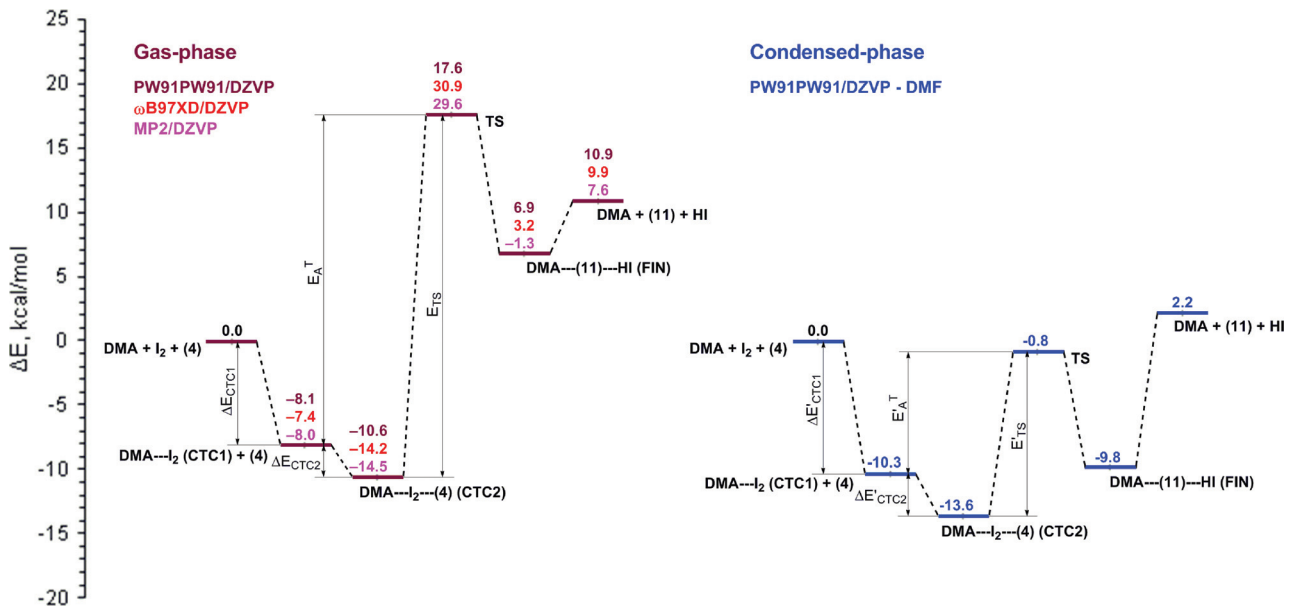


Fig. 2 The computed profile of potential energy for 3/iodanylium-de-hydronation of 2,3,3-trimethylbut-1-ene (**4**).

chemical shifts are referenced to tetramethylsilane as an internal standard and reported in parts per million (ppm). *N*,*N*-Dimethylacetamide 99+% was purchased from Acros. Triterpenoids (**1–3**) and 2-(1-adamantyl)propene (**7**) were obtained using previously developed procedures.[17–20] The other alkenes and reagents were purchased from Aldrich.

30-Iodolup-20-en-3β,28-diol (8)

Betulin (**1**) (4.43 g, 10.00 mmol) was dissolved in *N*,*N*-dimethylacetamide (176 ml) and stirred at 25 °C. Crystalline iodine (15.23 g, 60.00 mmol) was added to the solution in one portion. The reaction mixture was vigorously stirred for 1 min and poured immediately into a sodium bisulfite (22 g) solution in water (500 ml). The precipitate was filtered, washed with cold water (500 ml), then with hot water (60 °C, 500 ml) and dried in a vacuum oven (60 °C, 230 mm Hg), yielding the titled compound as a white powder (5.29 g, 94%), m.p. 163–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (s, 1H), 4.99 (s, 1H), 3.94 (dd, 2H), 3.81 (d, 1H), 3.33 (d, 1H), 3.19 (dd, 1H), 2.39–2.20 (m, 2H), 1.99–0.67 (m, 38H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.96, 112.03, 78.96, 60.34, 55.25, 50.54, 50.33, 47.81, 43.81, 42.71, 40.94, 38.85, 38.70, 37.21, 37.14, 34.25, 33.76, 33.07, 29.19, 27.98, 27.37, 26.99, 26.75, 20.92, 18.27, 16.11, 16.02, 15.36, 14.75, 11.79. ^{1}H NMR (300 MHz, CD_3OD): δ 5.18 (s, 1H), 5.00 (s, 1H), 4.01 (dd, 2H), 3.75 (d, 1H), 3.26 (d, 1H), 3.12 (dd, 1H), 2.44–2.21 (m, 2H), 2.00–0.67 (m, 38H). ^{13}C NMR (75 MHz, CD_3OD): δ 154.07, 112.35, 79.66, 60.20, 56.82, 51.83, 51.76, 49.03, 45.29, 43.86, 42.21, 40.08, 39.98, 38.65, 38.31, 35.52, 34.86, 34.21, 30.39, 28.64, 28.17, 28.12, 28.06, 22.11, 19.46, 16.76, 16.61, 16.16, 15.26, 11.61. Found: C, 63.32; H, 8.74; I, 22.02. Calc. for $C_{30}H_{49}IO_2$: C, 63.37; H, 8.69; I, 22.32.

30-Iodolup-20-en-3β,28-diol (8) (electrolysis)

Betulin (**1**) (1.00 g, 2.26 mmol) and urea (0.68 g, 11.30 mmol) were dissolved in *N*,*N*-dimethylacetamide (60 ml). The solution was stirred in an electrolyzer at 25 °C. Crystalline iodine (0.57 g, 2.26 mmol) was added to the solution and direct current (0.05 A, 18.96 V) was immediately applied to electrodes (platinum cathode and anode plates (2.5 cm × 2.5 cm), 0.5 cm distance between the plates). Electrolysis was stopped after 130 min. The reaction solution was poured into a sodium bisulfite solution (1 g) in water (200 ml). The precipitate was filtered, washed with cold water (100 ml), then with hot water (60 °C, 100 ml) and dried in a vacuum oven (60 °C, 230 mm Hg), yielding the titled compound as a white powder (1.22 g, 94%).

30-Iodo-3-oxolup-20-en-28-al (9)

Betulonic aldehyde (**2**) (4.41 g, 10.00 mmol) was dissolved in *N*,*N*-dimethylacetamide (55 ml) and stirred at 25 °C. Crystalline iodine (15.23 g, 60.00 mmol) was added to the solution in one portion. The reaction mixture was vigorously stirred for 10 min and poured immediately into a sodium bisulfite (22 g) solution in water (500 ml). The precipitate was filtered, washed with cold water (500 ml), then with hot water (60 °C, 500 ml) and dried in a vacuum oven (60 °C, 230 mm Hg), yielding the titled compound as a white powder (2.28 g, 93%), m.p. 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (d, 1H), 5.21 (s, 1H), 5.02 (s, 1H), 3.95 (dd, 2H), 2.89 (m, 1H), 2.55–2.34 (m, 2H), 2.23–0.93 (m, 37H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.96, 205.93, 151.61, 112.43, 59.34, 54.92, 49.80, 49.53, 47.32, 43.70, 42.61, 40.79, 39.64, 38.66, 36.89, 34.11, 33.66, 32.95, 32.85, 29.06, 28.84, 26.80, 26.62, 21.37, 21.02, 19.60, 15.99, 15.78, 14.20, 10.69. Found: C, 63.60; H, 8.08; I, 22.19. Calc. for $C_{30}H_{45}IO_2$: C, 63.82; H, 8.03; I, 22.48.

30-Iodo-3β-hydroxylup-20-en-28-oic acid (10)

Betulinic acid (**3**) (4.57 g, 10.00 mmol) was dissolved in *N*,*N*-dimethylacetamide (271 ml) and stirred at 25 °C. Crystalline iodine (15.23 g, 60.00 mmol) was added to the solution in one portion. The reaction mixture was vigorously stirred for 10 min and poured immediately into a sodium bisulfite (22 g) solution in water (500 ml). The precipitate was filtered, washed with cold water (500 ml), then with hot water (60 °C, 500 ml) and dried in a vacuum oven (60 °C, 230 mm Hg), yielding the titled compound as a white powder (4.34 g, 75%), m.p. 184–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19 (s, 1H), 5.00 (s, 1H), 3.95 (dd, 2H), 3.19 (dd, 1H), 2.99 (td, 1H), 2.32–0.67 (m, 39H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.76, 152.30, 112.21, 78.97, 56.27, 55.30, 51.10, 50.46, 43.35, 42.42, 40.69, 38.85, 38.71, 38.39, 37.20, 36.85, 34.33, 33.49, 32.01, 29.70, 27.98, 27.38, 26.56, 20.93, 18.27, 16.15, 16.08, 15.35, 14.71, 11.14. ^{1}H NMR (300 MHz, CD_3OD): δ 5.19 (s, 1H), 5.00 (s, 1H), 4.01 (dd, 2H), 3.15–3.00 (m, 2H), 2.35–0.69 (m, 39H). ^{13}C NMR (75 MHz, CD_3OD): δ 180.03, 154.46, 112.36, 79.68, 57.59, 56.90, 52.14, 52.03, 44.80, 43.63, 41.99, 40.12, 39.99, 39.74, 38.37, 37.94, 35.67, 34.71, 33.24, 30.92, 28.65, 28.08, 27.97, 22.23, 19.49, 16.79, 16.73, 16.16, 15.18, 11.31. Found: C, 61.64; H, 8.04; I, 21.52. Calc. for $C_{30}H_{47}IO_3$: C, 61.85; H, 8.13; I, 21.78.

2-Iodo-2-(*tert*-butyl)propene (11)

A fresh 1 M iodine solution in *N*,*N*-dimethylacetamide (12.00 ml, 12.00 mmol) was added to the stirred 2,3,3-trimethylbut-1-ene (**4**), (0.59 g, 6.00 mmol). The mixture was vigorously stirred at 25 °C for 4 min and poured into a sodium bisulfite (3.5 g) solution in water (100 ml). The resulting emulsion was extracted with pentane (2 × 50 ml). The combined organic phase was washed with water (50 ml), dried over sodium sulfate, filtered and evaporated in a vacuum, yielding the titled compound as an orange oil (0.34 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (s, 1H), 5.15 (s, 1H), 4.01 (s, 2H), 1.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.46, 115.55, 36.24, 29.89, 4.70. Found: C, 37.48; H, 5.80; I, 56.45. Calc. for $C_7H_{13}I$: C, 37.52; H, 5.85; I, 56.63.

1-Iodomethylcyclohexene (12)

Methylenecyclohexane (0.24 g, 2.50 mmol) was added to the solution of iodine (2.81 g, 14.99 mmol) in *N*,*N*-dimethylacetamide (3 ml). The mixture was vigorously stirred at 25 °C for 2 min and poured into a sodium bisulfite (6 g) solution in water (50 ml). The resulting emulsion was stirred and extracted with pentane (2 × 50 ml). The combined organic phase was

washed with water (50 ml), dried over sodium sulfate, filtered and evaporated in a vacuum, yielding the titled compound as an orange oil (0.31 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 (m, 1H), 3.90 (m, 2H), 2.16 (m, 2H), 1.93 (m, 2H), 1.72–1.51 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.46, 126.58, 27.12, 25.68, 22.42, 21.83, 14.82. Found: C, 37.98; H, 5.14; I, 56.97. Calc. for $C_7H_{11}I$: C, 37.86; H, 4.99; I, 57.15.

(3-Iodoprop-1-en-2-yl)benzene (13)

A fresh 1 M iodine solution in *N*,*N*-dimethylacetamide (12.00 ml, 12.00 mmol) was added to stirred α-methylstyrene (**6**) (0.71 g, 6.00 mmol). The mixture was vigorously stirred at 25 °C for 15 min and poured into a sodium bisulfite (3.5 g) solution in water (100 ml). The resulting emulsion was extracted with pentane (2 × 50 ml). The combined organic phase was washed with water (50 ml), dried over sodium sulfate, filtered and evaporated in a vacuum, yielding the titled compound as an orange oil (1.10 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.22 (m, 5H), 5.53 (s, 1H), 5.47 (s, 1H), 4.32 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.48, 137.80, 128.47, 128.27, 126.05, 115.60, 7.22. Found: C, 44.08; H, 3.86; I, 51.74. Calc. for C_9H_9I: C, 44.29; H, 3.72; I, 51.99.

2-(1-Adamantyl)-3-iodopropene (14)

A fresh 1 M iodine solution in *N*,*N*-dimethylacetamide (24.00 ml, 24.00 mmol) was added to stirred 2-(1-adamantyl)-propene (7) (1.06 g, 6.00 mmol). The mixture was vigorously stirred at 25 °C for 5 min and poured into a sodium bisulfite (7 g) solution in water (100 ml). The resulting emulsion was extracted with pentane (2 × 50 ml). The combined organic phase was washed with water (50 ml), dried over sodium sulfate, filtered and evaporated in a vacuum, yielding the titled compound as an orange oil (0.79 g, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.31 (m, 1H), 5.08 (m, 1H), 4.00 (s, 2H), 2.03 (m, 3H), 1.79–1.65 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.94, 115.39, 41.55, 38.17, 36.71, 28.55, 3.99. Found: C, 51.89; H, 6.46; I, 41.84. Calc. for $C_{13}H_{19}I$: C, 51.67; H, 6.34; I, 41.99.

General procedure for kinetic measurements

The quenching and analyzing technique was used to obtain reagent concentration/time data. The reaction time intervals were chosen for a betulin conversion less than 15% when no inhibition (related to the hydrogen iodide accumulation in the reaction media) was observed (up to 25–90 s); several sets of experiments were performed. Betulin (**1**) and iodine were dissolved separately in *N*,*N*-dimethylacetamide to form solutions containing a precisely known concentration of the reagents for each set of experiments. Determined volumes of the solutions were mixed (1 : 1, 1 : 1.2 and 1.2 : 1 betulin to iodine molar ratios) at a specified temperature (25, 35, 45, 55 and 65 °C) and stirred for a fixed period of time for each experiment. The mixture was immediately treated with aqueous sodium bisulfite solution to neutralize iodine and terminate the reaction. The precipitate was filtered, washed with water and dried. The solid samples from these experiments are mixtures of 30-iodolup-20-en-3β,28-diol (**8**) and starting betulin. They were dissolved in $CDCl_3$ and analyzed by ^{1}H NMR (500 MHz, Varian 500 with Auto-Tuner) to determine the content of (**8**) in the mixture. This value was used to determine the concentration of betulin and iodine at the moment of reaction termination. Kinetic data were analyzed by the least squares linear regression to find the corresponding functional correlations. The reaction order, rate constants, activation energy E_A, enthalpy $\Delta H^{\ddagger}_{298}$, entropy $\Delta S^{\ddagger}_{298}$ and Gibbs free energy $\Delta G^{\ddagger}_{298}$ were calculated using standard kinetic and thermodynamic equations. See ESI† for detailed kinetic experimental procedures and calculations.

Computational

Quantum mechanics calculations of the model reaction between 2,3,3-trimethylbut-1-ene (**4**) and iodine in *N*,*N*-dimethylacetamide were performed by using the Gaussian 03 program package.[21] Geometries of all structures were fully optimized at the PW91PW91,[22a–c] ωB97XD[23] and MP2[24a–c] levels of theory using the DZVP[25] basis set. Stationary points were confirmed to be minima or transition states (**TS**) by calculating the normal vibrations within the harmonic approximation. The reaction pathways along both directions from the transition structures were followed by the IRC[26a,b] method. All computed energies are corrected for zero-point vibrational energies (ZPVE). Additionally, single-point calculations including the solvent model (COSMO, DMF as a model solvent) were done with the Orca 2.6 program.[27]

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