

Rapid Communication

Development of aqua-soluble compounds based on vitamin A series molecules: Synthetic transformations of β -ionone

Solomon Libsu & Anil K Singh*

Department of Chemistry
Indian Institute of Technology Bombay
Powai, Mumbai 400 076, India
E-mail: retinal@chem.iitb.ac.in

Received 2 April 2007; accepted (revised) 14 May 2007

Several β -ionyl compounds bearing hydrophilic moieties like a carbohydrate, amine, phosphate and amino acid have been prepared and characterized. The solubilisation behaviour of these compounds has been examined by studying their UV-Vis absorption behaviour in micelles.

Keywords: β -Ionone, radioprotective agents, vitamin A compounds

Carotenoids and retinoids, particularly compounds in vitamin A series are involved in a wide range of life-sustaining biological processes like vision, light-induced proton transport, cell differentiation and growth, prevention of oxidative stress, regulation of the immune system and many others¹. The hydrophobic nature of these compounds has, however, been an impediment in some of their applications². Reported attempts to obviate this problem include liposomal encapsulation^{3,4} and attachment of solubilizing groups to them^{2,5,6}. *trans*- β -Ionone **1a** is a degraded C₁₃ sesquiterpene sharing important structural features with vitamin A and many carotenoids. It is widely used as an intermediate in the synthesis of vitamin A and perfume chemicals as well as several other natural products^{7,8}. Its utility in the synthesis of antileishmanial and antimalarial agents and its ability to inhibit the growth of malignant cells in different experimental models have been reported recently⁹⁻¹¹.

In light of these facts and the structural similarity of **1a** with vitamin A compounds, it was thought desirable to develop water-soluble derivatives of this compound, analogous to a few examples of such substances isolated from natural sources^{12,13}. In this context, **1a** has been chemically transformed into several interesting compounds including **1d-1g** (Figure 1).

Results and Discussion

Appropriate chemical transformations at C-4, C-10 and the carbonyl group of **1a** can lead to attachment of aqua-soluble moieties thereby enhancing the water-solubility of the parent compound. To this end, *trans*-4-hydroxy- β -ionone **1b** was synthesized *en route* to further elaboration, along with the formoxy compound **1c** as a side product, by a three-step sequence involving allylic bromination of **1a** followed by nucleophilic substitution with the formate ion and subsequent alkaline hydrolysis¹⁴. It may be mentioned here that **1b** was also prepared efficiently in a yield of 46% by subjecting the bromo-compound formed in the first step of the above sequence directly to a nucleophilic displacement reaction with water at RT thus not only avoiding the need to use the HCO₂Na/HCO₂H/Na₂CO₃ combination¹⁴ but also eliminating the additional task of purifying **1b** from the formate ester **1c**.

α -D-Glucos-conjugate **1d** was synthesized from **1b** and 2,3,4,6-tetra-O-benzoyl-D-glucopyranosyl bromide¹⁵ by a Koenigs-Knorr reaction as described elsewhere¹⁶. The ¹H NMR spectrum of this product distinctly exhibited signals that are ascribable to its sugar and aglycone portions. The doublet centered at δ 6.86 with a *J*-value of 3.6 Hz is assigned to the anomeric hydrogen. The magnitude of the *J*-value is suggestive of equatorial disposition¹⁷ for this hydrogen, a claim further corroborated by an absorption peak at 855 cm⁻¹ in the IR spectrum of the product¹⁸. The remaining glucose protons are well accounted for by the ¹H NMR spectrum, as are the hydrogens on the saturated carbon atoms of the β -ionyl moiety of **1d**. While the signal due to H-7 is obscured by the large number of aromatic protons in the region δ 7.26-8.18, H-8 is clearly revealed as a doublet at δ 6.19 with a coupling constant of 16.4 Hz. The magnitude of the coupling constant of the C-8 proton together with an absorption peak at 983 cm⁻¹ in the IR spectrum of the conjugate confirm that the *trans* stereochemistry about the C(7)-C(8) double bond of the ionyl portion remain intact. The ¹³C NMR spectrum of **1d** also accords quite well with the structure shown. The ester carbonyl carbon atoms are huddled together in the range δ 166.14-164.46, as are

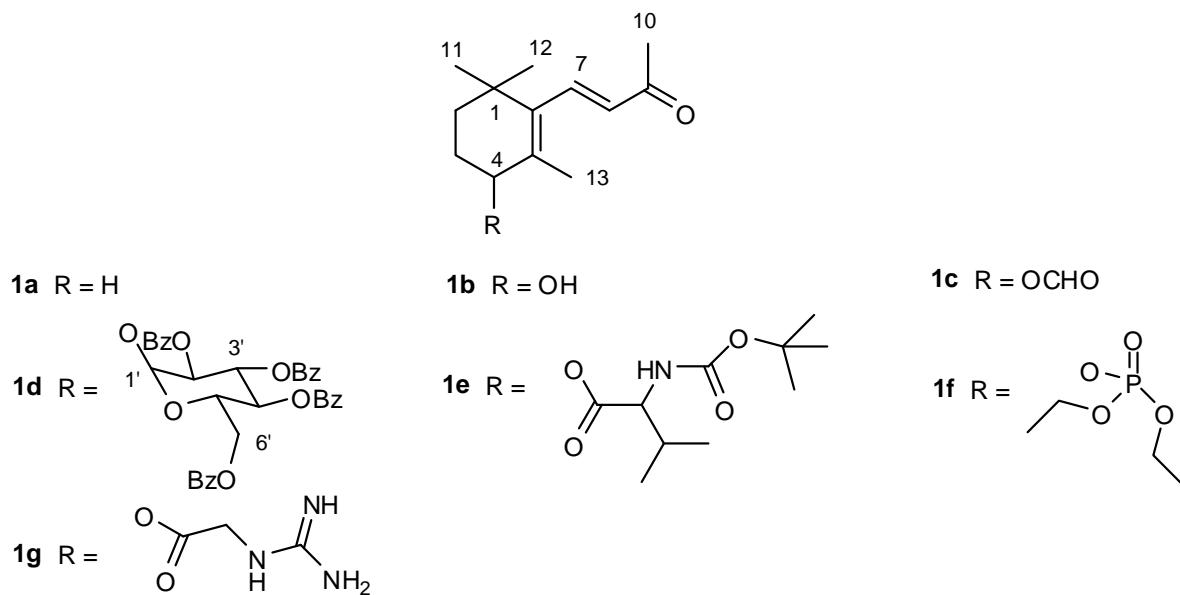


Figure 1 — Chemical structures of synthesized β -ionyl compounds **1b** -**1g**

five of the carbons of the glucose portion in the region δ 70.60- 62.58, with the anomeric carbon appearing at δ 90.15. Furthermore, the ^{13}C -signals in the range δ 133.96-128.44 together with an additional absorption peak at δ 140.53 are reflective of the twenty distinct sp^2 (olefinic and aromatic) carbon atoms possessed by **1d**. While the signal due to C-4 of the ionyl portion of the conjugate is thought to be overlapping with the solvent (CDCl_3) peaks, that due to the carbonyl carbon atom (C-9) has apparently not been discernible, though its presence is readily elicited from a singlet at δ 2.35 (C-10 hydrogens) and an absorption peak appearing as a shoulder at 1675 cm^{-1} in the ^1H NMR and infrared spectra, respectively, of the compound. It is noteworthy that a carbonyl carbon atom eluding detection by ^{13}C NMR spectroscopy is not unprecedented¹². The mass spectrum of **1d** did not show an ion peak at m/z 786 expected for the molecular ion $[\text{C}_{47}\text{H}_{46}\text{O}_{11}]^+$. It did display, however, a base peak at m/z 579.1 ascribable to the sugar portion resulting from fracture of the parent molecule at the glycosidic bond as well as peaks at m/z 207, 189.1 and 108.1 that can reasonably be associated with fragment ions emanating from the aglycone part of the molecule.

In a further endeavour, **1b** was also allowed to undergo, in separate experiments, a DCC promoted esterification¹⁹ reaction with N-Boc-L-valine and phosphorylation²⁰ with triethyl phosphite to afford,

respectively, amino acid ester **1e** and phosphate ester **1f**. The former conjugate was obtained as a mixture of stereoisomers as suggested by some closely spaced peaks in its ^1H and ^{13}C NMR spectral data. Resonance lines of protons on the ionyl portion of **1e** are observed at δ 7.18 (d, $J=16.4$ Hz, H-7), 6.13 (d, $J=16.4$ Hz, H-8), 4.23 (m, H-4), 2.32 (s, H-10), 1.71 (s, H-13), and 1.05, 1.09 (s, s, H-11, H-12). Likewise, the protons of the Boc-valine moiety of **1e** are revealed at δ 1.45 (s, *t*-Bu), 1.00 and 0.98 (d, d, $J=2.4$ and 2.8 Hz, $\text{CH}(\text{CH}_3)_2$), 5.03 (d, $J=8.8$ Hz, NH), and 5.26 (m, CHNH). In conformity with the structure shown for **1e**, its ^{13}C NMR spectrum displayed signals, amongst others, at δ 198.14, 172.24(d), 156.67, 155.74, 142.06(t), 133.46, 129.31(d), 79.98(d), 72.94(d) and 58.84(t). The mass spectrum of **1e** displayed a pseudo-molecular ion peak at m/z 430.2 ($\text{M}^+ + \text{Na}$).

The spectral data obtained for **1f** are also in line with the structure shown. Seventeen resonance lines in its ^{13}C NMR spectrum included peaks at δ 198.61, 142.87, 139.47, 134.21, 133.21, 70.00, 63.82 and 63.77. All the hydrogens of phosphate **1f** are also fully accounted for by its ^1H NMR spectrum which exhibited, *inter alia*, peaks at δ 7.20 (d, $J=16.4$ Hz, H-7), 6.13 (d, $J=16.4$ Hz, H-8), 4.15 (m, $2 \times \text{OCH}_2$), 4.02 (t, $J=4.4$ Hz, H-4), 2.31 (s, H-10), 1.85 (s, H-13), 1.35 (t, OCH_2CH_3), and 1.08, 1.05 (s, s, H-11, H-12). The appearance of a single peak at δ -2.70 in ^{31}P NMR

spectrum confirmed incorporation of phosphate moiety in the conjugate. Lack of a method for the selective removal of the ethyl groups precluded conversion of **1f** into the corresponding phosphoric acid derivative. An alternative was thus sought in an Arbuzov type reaction at RT of *trans*-4-bromo- β -ionone²¹ and triethyl phosphite with the intention of getting the corresponding phosphonate. However, the reaction led to a product having the same spectral characteristics as **1f**. A further attempt to introduce a phosphoric acid moiety at C-4 of **1a** via phosphorylation of **1b** with phosphorous oxychloride followed by hydrolysis of the reaction mixture did not yield the anticipated compound. The product isolated from this reaction turned out to be 4-oxo-*trans*- β -ionone.

In a further attempt to functionalize C-4 of **1a**, *trans*-4-bromo- β -ionone²¹ was allowed to undergo nucleophilic substitution reaction with guanidinoacetic acid to afford imino-ester **1g**. The ¹H NMR spectrum of **1g** bore signals at δ 7.17 (d, *J*=16.4 Hz, H-7), 6.03 (d, *J*=16.4 Hz, H-8), 4.02 (q, *J*=7.2 Hz, O₂CCH₂NH), 3.92 (t, *J*=4.8 Hz, H-4), 2.22 (s, H-10), 1.75 (s, H-13), 1.16 (t, *J*=6.8, 7.6 Hz, CH₂NH), 0.98 and 0.95 (s, s, H-11, H-12). The three terminal imino hydrogens (C (NH) NH₂) have apparently coalesced into a singlet at δ 1.95. Included in the ¹³C NMR spectrum of **1g** are signals located at δ 198.99, 173.61, 171.38, 69.53 and 60.47 whilst a strong peak at 3420 cm⁻¹ in its IR spectrum is assertive of the NH groupings. The mass spectrum of **1g** exhibited, among others, an ion peak at *m/z* 263.1 (M⁺-44). An analogous attempt to attach ascorbic acid to C-4 of **1a** via a nucleophilic substitution reaction of an aqueous solution of sodium L-ascorbate with *trans*-4-bromo- β -ionone²¹ was unsuccessful. The reaction yielded, instead, alcohol **1b** along with an unidentified material.

To get an idea about solubility, localisation and translocation of these compounds through biological membranes, the UV-Vis absorption spectra of these compounds have been examined in membrane mimetic system of micelles. The λ_{max} of **1a** in reverse micelle of sodium bis(2-ethylhexyl) sulphosuccinate (AOT) is the same as that in the hydrocarbon solvent *n*-heptane (**Table I** and **Table II**). However, polar environment causes red shift in its λ_{max} . In normal micelle of cetyltrimethyl ammonium bromide (CTAB), it gets anchored in relatively polar environment. On the other hand, the λ_{max} of hydroxy

ketone **1b** and phosphate ester **1f** shifted slightly to a longer wavelength (278 nm) in the AOT reverse micelle with ω = 6, 8, 10, 12 relative to their λ_{max} value of 275/276 nm in the non-polar solvent *n*-heptane (**Table I**). The imino ester **1g** likewise experienced a red shift of 2 nm in its λ_{max} value from 276 nm in *n*-heptane (**Table I**) to 278 nm in reverse micelle of ω = 10, 12 (**Table II**).

Based on the absorption data in **Tables I** and **II**, it can be said that while **1a** is completely engulfed by the bulk organic solvent of the AOT/hexane/water system, compounds **1b**, **1f**, and **1g** are embedded in the interfacial region of the reverse micelle with their polar groups oriented towards the water pool. The absence of any discernible absorption maximum for gluco-conjugate **1d** and amino acid ester **1e** in either micelle [CTAB (aq)] or H₂O (**Table I**) lends itself to suggest that these derivatives are apparently more hydrophobic than the parent ketone **1a**. Attempts to debenzoylate **1d** with ammonia gas have proved unsuccessful. These observations are interpreted in terms of slightly better aqua-solubility of **1b**, **1f** and **1g** relative to the parent compound **1a**, a result ascribable to the solubilising effect of the polar moieties these derivatives bear.

In conclusion, β -ionyl structure has been further functionalized leading to several interesting compounds with altered hydrophilicity. Thus, this work gives a new direction towards developing aqua-soluble retinoids with potentially useful biological properties like antioxidant and radioprotection.

Experimental Section

All the chemicals and solvents used in this work were procured from suppliers in Mumbai, India. Solvents used were purified and dried following standard procedures. Petroleum ether used was of 60-80°C range. ¹H and ¹³C NMR spectra were recorded with a Varian VXR 400 MHz FTNMR instrument using TMS as internal standard. Mass spectra were recorded on a Micromass Q-TOF micro instrument. FTIR spectra were recorded with Nicolet Impact-400 series spectrophotometer. UV-Vis absorption spectra were recorded on a Shimadzu UV-160A or JASCO V-570 UV/VIS/NIR spectrophotometer.

1.0 \times 10⁻² M CTAB normal micelles were prepared by dissolving CTAB in distilled water. β -Ionyl compounds were added to this solution, which was further stirred for a few minutes to obtain a clear

Table I — UV-Vis absorption data of **1a**, **1b**, **1d-1g** in CTAB micelle and solvents of varying polarity

| Compd | Solvent | λ_{\max} nm | Compd | Solvent | λ_{\max} nm | Compd | Solvent | λ_{\max} nm |
|-----------|------------------------|---------------------|-----------|------------------------|---------------------|-----------|------------------------|---------------------|
| 1a | <i>n</i> -Heptane | 282 | 1d | <i>n</i> -Heptane | 276 | 1f | <i>n</i> -Heptane | 276 |
| | Acetonitrile | 289 | | Acetonitrile | 274 | | Acetonitrile | 282 |
| | Methanol | 295 | | Methanol | 274 | | Methanol | 285 |
| | CTAB ^a (aq) | 300 | | CTAB ^a (aq) | hs | | CTAB ^a (aq) | 288 |
| | Water | 304 | | Water | hs | | Water | 288 |
| 1b | <i>n</i> -Heptane | 275 | 1e | <i>n</i> -Heptane | 272 | 1g | <i>n</i> -Heptane | 276 |
| | Acetonitrile | 281 | | Acetonitrile | 278 | | Acetonitrile | 280 |
| | Methanol | 288 | | Methanol | 278 | | Methanol | 284 |
| | CTAB ^a (aq) | 290 | | CTAB ^a (aq) | hs | | CTAB ^a (aq) | 286 |
| | Water | 290 | | Water | hs | | Water | 286 |

^a [CTAB] = 1.0×10^{-2} M. (hs: hardly soluble).

Table II — UV-Vis absorption data of **1a**, **1b**, and **1d-1g** in AOT reverse micelles

| Compd | Solvent ^b $\omega = [\text{H}_2\text{O}]/[\text{AOT}]$ | λ_{\max} nm | Compd | Solvent ^b $\omega = [\text{H}_2\text{O}]/[\text{AOT}]$ | λ_{\max} nm |
|-----------|---|---------------------|-----------|---|---------------------|
| 1a | 2-12 | 282 | 1e | 2-12 | 270-272 |
| 1b | 2-12 | 276-278 | 1f | 2-12 | 276-278 |
| 1d | 2-12 | 272-274 | 1g | 2-12 | 276-278 |

^b AOT/*n*-hexane (1.0×10^{-2} M) reverse micelle of varying hydration degree (ω , molar ratio of $[\text{H}_2\text{O}]/[\text{AOT}]$).

solution. For reverse micellisation, the β -ionyl compound was added to *n*-hexane solution of AOT (1.0×10^{-2} M) containing water required for a specific ω (molar ratio of $[\text{H}_2\text{O}]/[\text{AOT}]$). The mixture was carefully hand-shaken to obtain a clear solution for absorption studies. The final concentration of the β -ionyl compound was maintained at 1.0×10^{-5} M.

4-Hydroxy- β -ionone, **1b**

1b was prepared by following the reported procedure¹⁴. In addition, it is found that it can also be prepared in 46% yield by subjecting the bromo-compound formed in the first step of the reported procedure directly to a nucleophilic displacement reaction with water at RT thus not only avoiding the need to use the $\text{HCO}_2\text{Na}/\text{HCO}_2\text{H}/\text{Na}_2\text{CO}_3$ combination but also eliminating the additional task of purifying **1b** from the formate ester **1c**. In the new procedure, to a warm solution of **1a** (1.2 g, 6 mmol) in carbon tetrachloride (20 mL) was added freshly purified N-bromosuccinimide (1.25 g, 7 mmol) and catalytic amount of benzoyl peroxide. After refluxing for 1.5 hr, the mixture was cooled to 0°C and petroleum ether (10 mL) was added to it. The reaction mixture was then filtered and most of the

solvents removed under reduced pressure. The contents of the flask were taken up in water containing little 1,4-dioxane and stirred overnight at RT. Usual work-up involving extraction of organic matter with dichloromethane, drying with anhydrous sodium sulphate followed by removal of dichloromethane under reduced pressure yielded dark brown oil. Column chromatography (silica gel, 10% ethyl acetate-petroleum ether) of the dark brown oil afforded **1b** in 46% yield (0.53 g) as light brown oil. The compound so obtained exhibited spectral data (IR, ^1H NMR) as reported earlier^{13,22}. In addition, it showed the following ^{13}C NMR (CDCl_3) data: δ 198.81, 143.07, 139.33, 134.40, 133.11, 69.92, 34.82, 34.76, 28.93, 28.40, 27.66, 27.45, 18.62.

(E)-2-(Benzoyloxymethyl)-6-(2,4,4-trimethyl-3-(3-oxobut-1-enyl)cyclohex-2-enyloxy)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate, **1d**

A mixture of 2,3,4,6-tetra-O-benzoyl-D-glucopyranosyl bromide (0.73 g, 1.11 mmol) prepared as described elsewhere¹⁵ and **1b** (0.25 g, 1.2 mmol) in dry acetonitrile (25 mL) was subjected to a mercuric bromide (0.36 g, 1.0 mmol) catalysed Koenigs-Knorr

coupling reaction following a literature procedure¹⁶. Purification of the crude reaction mixture by silica gel column chromatography using 10% ethyl acetate in petroleum ether as eluent afforded 63 mg (7%) of conjugate **1d** as a dark brown solid, m.p. 140°C (dec.); IR (KBr): 2959, 2926, 2867, 1731, 1675, 1270, 983, 855, 706 cm⁻¹; ¹H NMR (CDCl₃): δ 1.19, 1.15 (s, s, 6H, H-11 and H-12), 1.80 (s, 3H, H-13), 2.54, 1.83 (m, 4H, H-3 and H-2), 2.35 (s, 3H, H-10), 4.47-4.51 (m, 1H, H-6'), 4.61-4.66 (m, 2H, H-5', H-6'), 5.69 (dd, 1H, H-2'), 5.88 (t, *J* = 10.0, 9.6 Hz, 1H, H-4'), 6.19 (d, *J* = 16.4 Hz, 1H, H-8), 6.33 (t, *J* = 10.0 Hz, 1H, H-3'), 6.86 (d, *J* = 3.6 Hz, 1H, H-1'), 8.18-7.26 (m, Ar-protons and H-7); ¹³C NMR (CDCl₃): δ 26.80, 27.39, 29.76, 34.24, 34.27, 37.43, 42.35, 62.58, 68.99, 70.56, 70.57, 70.60, 76.57, 90.15, 128.44, 128.47, 128.50, 128.68, 128.83, 128.86, 128.95, 129.11, 129.66, 129.81, 129.86, 129.91, 129.96, 130.09, 133.17, 133.40, 133.53, 133.57, 133.96, 140.53, 164.46, 165.21, 165.42, 165.98, 166.14; MS: *m/z* (%) 189.1 (13), 207 (9), 231.0 (39), 579.1 (100).

(E)-2,4,4-Trimethyl-3-(3-oxobut-1-enyl)cyclohex-2-enyl 2-(*tert*-butoxycarbonylamino)-3-methylbutanoate, 1e

Compound **1e** was prepared following a literature procedure for esterification reactions¹⁹. A solution of N-Boc-L-valine (0.5 g, 2.3 mmol), N,N-dicyclohexylcarbodiimide (0.5 g, 2.4 mmol), **1b** (0.5 g, 2.4 mmol) and 4-dimethylamino-pyridine (0.03 g, 0.25 mmol) in dichloromethane (25 mL) was stirred at RT for 3 hr during which time the starting hydroxy compound was consumed completely (TLC). Column chromatographic purification of the syrupy mixture obtained after work-up using 10% ethyl acetate/petroleum ether as an eluent led to isolation of **1e** as a yellow semisolid in a yield of 0.5 g (48%). ¹H NMR (CDCl₃): δ 1.00 and 0.98 (d, d, *J*=2.4 and 2.8 Hz, 6H, CH(CH₃)₂), 1.09, 1.05 (s, s, 6H, H-11 & H-12), 1.45 (s, 9H, *t*-Bu), 1.71 (s, 3H, H-13), 2.32 (s, 3H, H-10), 4.23 (m, 1H, H-4), 5.03 (d, *J*=8.8 Hz, 1H, NH), 5.26 (m, 1H, NHCH), 6.13 (d, *J* = 16.4 Hz, 1H, H-8), 7.18 (d, *J* = 16.4 Hz, 1H, H-7); ¹³C NMR (CDCl₃): δ 17.23, 17.49, 18.42, 18.53, 19.25, 24.61, 25.08, 27.51, 28.27, 28.31, 28.76, 31.28, 34.52, 58.84 (t), 72.94 (d), 79.98 (d), 129.31 (d), 133.46, 142.06 (t), 142.24, 155.74, 156.67, 172.24 (d), 198.14; MS: *m/z* (%) 191.1 (13), 243.2 (21), 299.2 (5), 430.2 (38) [M⁺ Na]⁺.

(E)-Diethyl 2,4,4-trimethyl-3-(3-oxobut-1-enyl)cyclohex-2-enyl phosphate, 1f

Compound **1f** was prepared following a literature procedure for phosphorylation reaction of alcohols²⁰. Thus, compound **1f** was obtained as a yellow viscous liquid from a reaction, performed at 0°C, of **1b** (0.16 g, 0.77 mmol) and triethylphosphite (0.15 g, 0.92 mmol) in a yield of 0.05 g (20%). IR (CHCl₃): 2940, 2869, 1673, 1367, 1260, 1036, 985, 827, 807, 548 cm⁻¹; ¹H NMR (CDCl₃): δ 1.08, 1.05 (s, s, 6H, H-11 and H-12), 1.35 (t, 6H, 2 × OCH₂CH₃), 1.45, 1.70, 1.92 (m, m, m, 4H, H-2 and H-3), 1.85 (s, 3H, H-13), 2.31 (s, 3H, H-10), 4.02 (t, *J*=4.4 Hz, 1H, H-4), 4.15 (m, 4H, 2 × OCH₂), 6.13 (d, *J*=16.4 Hz, 1H, H-8), 7.20 (d, *J*=16.4 Hz, 1H, H-7); ¹³C NMR (CDCl₃): δ 16.25, 16.31, 18.63, 27.51, 27.65, 28.45, 28.97, 29.80, 34.81, 63.77, 63.82, 70.00, 133.21, 134.21, 139.47, 142.87, 198.61; ³¹P NMR (CDCl₃): δ -2.70; MS: *m/z* (%) 127.0 (60), 155.1 (92), 183.1 (100), 205.1 (48), 329 [M⁺-15].

(E)-2,4,4-Trimethyl-3-(3-oxobut-1-enyl)cyclohex-2-enyl 2-guanidinoacetate, 1g

Compound **1g** was obtained as yellow oil in 25% yield from a RT reaction of *trans*-4-bromo-β-ionone and guanidinoacetic acid by adopting a literature procedure for a related preparation²¹. IR (CHCl₃): 3420, 2960, 2938, 2858, 1671, 1607, 1451, 1362, 1257, 1176, 1146, 1077, 1028, 999, 925, 877 cm⁻¹; ¹H NMR (CDCl₃): δ 0.98, 0.95 (s, s, 6H, H-11, H-12), 1.16 (t, *J*=7.6, 6.8 Hz, 1H, CH₂NH), 1.62, 1.36 (m, m, 4H, H-2 and H-3), 1.75 (s, 3H, H-13), 1.95 (s, 3H, C(NH)NH₂), 2.22 (s, 3H, H-10), 3.92 (t, *J*=4.8 Hz, 1H, H-4), 4.02 (q, *J*=7.2 Hz, 2H, CH₂NH), 6.03 (d, *J*=16.4 Hz, 1H, H-8), 7.17 (d, *J*=16.4 Hz, 1H, H-7); ¹³C NMR (CDCl₃): δ 18.48, 27.19, 27.65, 28.24, 28.72, 34.57, 34.86, 60.47, 69.53, 132.79, 134.96, 138.80, 143.36, 171.38, 173.61, 198.99; MS: *m/z* (%) 107.1 (36), 135.1 (100), 191.2 (12), 231.2 (9.6), 263.1 (1.2) [M⁺-44].

Acknowledgement

Financial support to this work from the Board of Research in Nuclear Sciences (Department of Atomic Energy, Government of India) and a Research Fellowship to Mr. Solomon Libsu by the Government of the Federal Democratic Republic of Ethiopia is gratefully acknowledged.

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