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From (*E*)- and (*Z*)-ketoximes to *N*-sulfenylimines, ketimines or ketones at will. Application to erythromycin derivatives

Jorge Esteban, Anna M. Costa,* Fèlix Urpí and Jaume Vilarrasa*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain

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Abstract—Reactions of (*E*)- and (*Z*)-ketoximes with trialkylphosphines and diphenyl disulfide (PhSSPh) have been compared to gain insight into the mechanisms involved and their potential applications. *N*-Sulfenylimine isomers and ketimines have been spectroscopically characterised. Both the *E* and *Z* isomers of erythromycin A oxime, when treated with Bu_3P and PhSSPh (1:4:8 ratio), give the same *N*-phenylsulfenyl ketimine (of configuration *E*) as the major compound, whereas with Bu_3P or Me_3P and PySeSePy (1:8:4 ratio) afford the imine in good yield. Clarithromycin oxime behaves similarly.
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Oximes are at the crossroad of the chemistry of carbonyl groups and nitrogen functional groups.[1] Recovery of carbonyl compounds from the corresponding oximes, when the latter have been used to protect[2] or purify the former, or when oximes have been obtained by other routes, is a subject of continuous interest.[3] Whereas N–O bonds of hydroxylamines are easily cleaved by reducing agents and whereas C=N bonds of imines are readily hydrolysed, the C=N–OH group is a robust, relatively stable substructure. In this connection, the work carried out by Zard and co-workers[4] on the use of tributylphosphine and diphenyl disulfide is remarkable: ketoximes react at rt with Bu_3P/PhSSPh,[5] to afford, besides Bu_3P=O, ketimines and/or *N*-phenylthio ketimines (usually called sulfenylimines or sulfenimines);[6] these imines or imine derivatives may be then hydrolysed to ketones during the workup or converted to other compounds.[4] Much more recently Lukin and Narayanan[7] have demonstrated, on $O^{2'},O^{4''}$-dibenzoyl erythromycin A oxime, that its sulfenylimine is the first long-lived intermediate and that it is slowly cleaved in situ by Bu_3P (in the presence of a proton source, such as benzenethiol) to give the imine.

When a similar reaction was performed[8] with equimolar amounts of cyclopentadecanone oxime **1a**, Me_3P and PhSSPh, in THF at rt, and the final mixture was directly separated by column chromatography on alumina or was first quenched with water buffered at pH 10 and extracted, *N*-(phenylsulfenyl)cyclopentadecanimine (*N*-SPh derivative **1b**)[9] was the major product; imine **1c** was not detected but ketone **1d** was isolated as a minor compound. On the other hand, using an excess of Me_3P and quenching the reaction with neutral water, **1d** was mainly obtained.[8] Thus, the cleavage of the N–S bond of **1b** (mediated by remaining Me_3P) was slow in the reaction medium or during the basic workup, but it took place rapidly in THF–H_2O.[10] Moreover, a pure sample of **1b**, treated in a NMR tube ($CDCl_3$) with a THF solution of Me_3P, allowed us to detect immediately imine **1c**,[11] which was only fully converted into ketone **1d** when a drop of water was added. All these facts may be summarised as in Scheme 1 (where HX means any proton source present or added, either PhSH, remaining oxime or water),[12] which complements previous results.[4,7,8] We describe here how to drive the process towards one or another compound as well as stereochemical details of the first step.

To favour the percentage of **1b**—to stop the sequence at the stage of **1b**—we repeated the reaction with a less active phosphine (Bu_3P, 1.2 equiv)[13] and an excess of PhSSPh (2.4 equiv), which afforded **1b** almost quantitatively. The four anhydrous solvents checked (THF, CH_3CN, CH_2Cl_2 or $CHCl_3$) gave the same result.

Keywords: Oximes; Sulfenylimines; Ketone protecting groups; Macrolide antibiotics; Erythromycin A; Clarithromycin.

* Corresponding authors. Tel.: +34-934021258; fax: +34-933397878; e-mail: jvilarrasa@ub.edu

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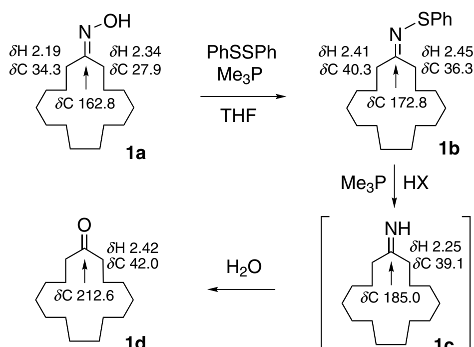
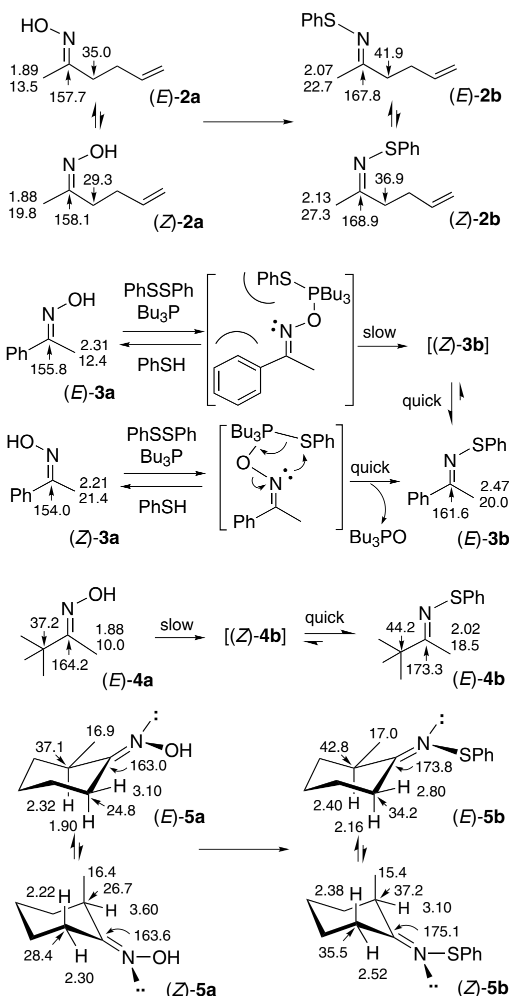


Scheme 1. Preliminary results. NMR spectral data in $CDCl_3$.[12]

To check the scope of these experiments, a few non-symmetric ketones were transformed, by known procedures, to oximes **5a**–**4a**. The reactivity of their *E* and *Z* isomers with Bu_3P plus PhSSPh was compared to gain insight into the first steps of these reactions. The main results are summarised in Scheme 2.



Scheme 2. Reagents and conditions: Bu_3P (1.2 equiv) and PhSSPh (2.4 equiv), 0.1–0.2 M THF solutions, 0–20 °C. Relevant ^1H and ^{13}C chemical shifts in $CDCl_3$ are indicated.[12]

Hex-5-en-2-one oxime **2a**, an *E*–*Z* mixture (65:35 in $CDCl_3$, 55:45 in THF-d_8, 70:30 in CD_3CN), when sulfenylated in THF at 0 °C with Bu_3P and excess of PhSSPh for 1 h, afforded (*E*)-**2b** plus (*Z*)-**2b** (75:25 ratio in $CDCl_3$, 80:20 in THF-d_8, 80:20 in CD_3CN) in excellent yield; the isomer ratios just indicated were kept after heating **2a** as well as **2b** overnight at 50 °C and registering again the spectra at 18 °C. Thus, they must be the equilibrium ratios at rt between the respective isomers.[14] When the NMR spectra of **1a**, (*E*)-**2a**, (*Z*)-**2a** and their sulfenylimines were compared, regular trends could be observed (see Scheme 2), among which we should highlight the downfield shifts of several ppm (7–10 ppm) that undergo the relevant δC values of the sulfenylimines as well as the expected fact that the δC values of methyl and methylene groups *anti* to the hydroxy and phenylthio groups are always higher than those of the corresponding *syn* groups, as known (steric compression).

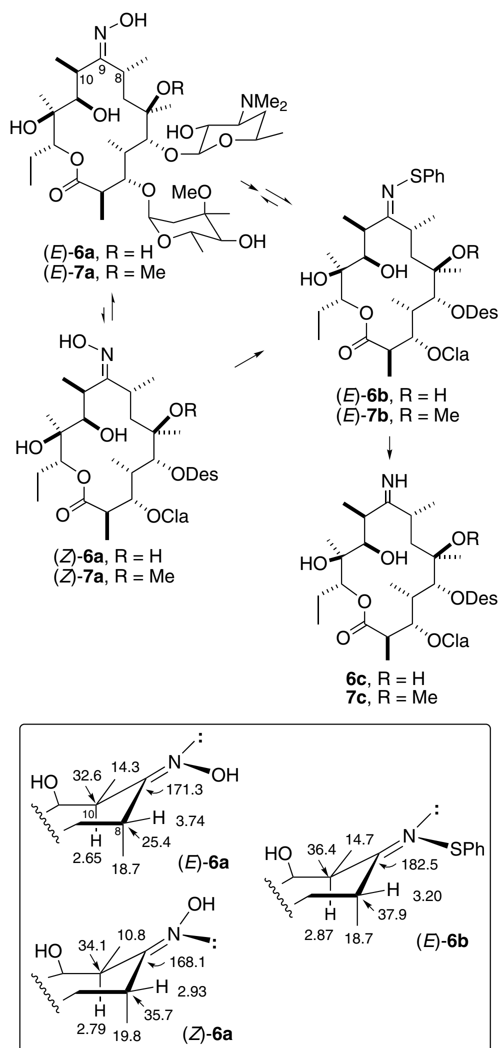
Acetophenone oxime, (*E*)-**3a**, when treated with Bu_3P (1.2 equiv) and PhSSPh (2.4 equiv) at 0 °C or at rt for several hours, gave only a trace of sulfenylimine; most of the starting oxime was recovered after the workup. By sharp contrast, its less stable isomer, (*Z*)-**3a**,[15] quickly afforded (*E*)-**3b** under the same conditions (Scheme 2). To force the conversion of (*E*)-**3a** to sulfenylimine a much larger reagent concentration was required: only when (*E*)-**3a** was stirred with 4 equiv of Bu_3P and 8 equiv of PhSSPh at 20 °C did we obtain (*E*)-**3b** in excellent yield, after 1 h of reaction. This sulfenylimine was known[16] and our spectral data were coincident with those reported. Indeed, only the *E* isomer of **3b** was seen by NMR in all trials (the methyl carbon of the sulfenylimine *E*, at 20.0 ppm, can be related, as explained in the preceding paragraph, to the chemical shift of 12.4 ppm for the methyl carbon of oxime *E*, whereas for the methyl carbon of sulfenylimine *Z*, if it had been obtained, a chemical shift around 28 ppm would be expected). We confirmed the reactivity differences by mixing samples of (*E*)-**3a** and (*Z*)-**3a** and subjecting the mixture to sulfenylation (under the mild conditions of Scheme 2); we noted that oxime *Z* disappeared, to give (*E*)-**3b**, while (*E*)-**3a** remained. In this case the equilibrium between the oxime isomers is very slow (and, if established on heating and/or under basic catalysis, it is largely shifted towards isomer *E*). The reactivity difference between the two isomers may be explained by the different steric hindrance around the nitrogen atom lone pairs of the plausible intermediates (as drawn in Scheme 2) and/or by the higher or lower strength of the N–O bonds depending on the electronic conjugation. We propose that a configuration inversion occurs, either via an intramolecular SPh transfer or by an intermolecular process involving the relative excess of sulfenylating agent. Probably such a configuration inversion takes place in most cases, although it cannot be obviously noted if only one compound is possible (from **1a** to **1b**) and it is very difficult to monitor and prove when the isomeric equilibria are more rapid than the sulfenylation reaction (as in the conversion of **2a** to **2b**) or when the equilibrium between the two sulfenylimines is completely shifted towards isomer *E* (as in the case of **3b**).

The relative significance of the steric effects was checked with pinacolone oxime [(*E*)-3,3-dimethylbutan-2-one oxime, (*E*)-**4a**].[17] Under the mild conditions of Scheme 2, it hardly reacted. As in the case of (*E*)-**3a**, we had to increase four times the concentration of both Bu_3P and PhSSPh to observe reaction rates similar to those of oximes **1a** and **2a**. Also, we only detected and isolated the *E* sulfenylimine, (*E*)-**4b**. We suggest in Scheme 2 that it is due to the expected fact that the *E*–*Z* equilibrium is more shifted than ever towards the less congested isomer. Thus, the close parallelism between the reactions of pinacolone and acetophenone derivatives indicates, at least, that there is one rate-limiting step in which the steric effects are important.

2-Methylcyclohexanone oxime **5a**, an *E*–*Z* mixture (ca. 90:10 in $CDCl_3$), when treated at 0 °C with Bu_3P/PhSSPh for 1 h, gave an *E*–*Z* mixture of **5b** (75:25 in $CDCl_3$) in ca. 80% yield. In agreement with a conformational study of (*Z*)-**5a**,[18] we noted that (*Z*)-**5b** prefers the $^4C_1$ conformation (with an axial methyl group), thus avoiding the steric hindrance that would result in the other chair conformation (with an equatorial methyl group and a *syn* NOH). Secondly, the rigid *chair* conformations allowed us, in addition, to use as relevant data also the δH of the axial and equatorial hydrogen atoms, more or less shifted downfield depending on their proximity to the heteroatoms (when in the preceding examples we only saw mean chemical shifts for the methylene hydrogens and no significant changes from oximes to sulfenylimines); in the present case, the equatorial hydrogen atoms near the OH group showed the highest δH values. Thirdly, the α methylene carbon atoms follow the general trend already mentioned in previous examples for the α carbon atoms (a downfield shift of several ppm—between 5.7 and 10.5 ppm until now—from each oxime to its analogue sulfenylimine). Fourthly, it is clear that the 2-Me carbon atoms do not show significant changes among them and with respect to the Me carbon atom of the parent compound 2-methylcyclohexanone (ca. 15 ppm), probably as no important steric compression effects do exist in the four structures depicted.

With these results in hand, we could tackle the more complex substrates that really attracted our attention, the oximes of macrolide antibiotics erythromycin A and clarithromycin.[19] Erythromycin A (*E*)-oxime, (*E*)-**6a**, the common EA oxime, treated in THF at 0 °C for 1 h with an excess of Bu_3P and PhSSPh (1:4:8 ratio), gave a mixture in which no oxime remained; the main and less polar spot on TLC was a *N*-SPh derivative, **6b**, and the more polar and very minor one could be the imine, **6c**, according to the MALDI MS spectra. With lower concentrations of reagents the reaction was not complete—with only 200 mol % of Bu_3P, the *N*-SPh derivative was hardly detected—as in the previous cases of oximes with sterically crowded nitrogen atoms and/or as if the free hydroxy groups of **6a** had consumed some equivalents of the reagent mixture to give rise to the corresponding phosphonium alkoxides (fortunately without further reactions). Separation of the reaction mixture by pouring it into an excess of aqueous K_2CO_3, filtering and dissolving the precipitate in EtOAc, followed by chromatography on alumina, a *N*-SPh derivative, **6b**, could be isolated in 40–50% yields, while imine **6c** (see below) was later eluted and obtained in 20–30% yields. That is to say, the sulfenylimine had been formed in high yields, but it was partially cleaved and/or hydrolysed to the imine during the isolation procedure. The well-known stability towards hydrolysis of erythromycin-related imines[20] explains why **6c** survived during the isolation procedure.

The *Z* oxime, (*Z*)-**6a**,[21] treated separately under identical conditions gave the same *N*-SPh derivative, **6b**, and imine **6c** as a minor compound. Comparison of the NMR parameters of the product **6b** with those of the two oximes[22] (Scheme 3), as well as with those of (*E*)-**5a** and (*E*)-**5b** (Scheme 2), suggested that, as expected, it was (*E*)-**6b**, bearing in mind: (i) the ^{13}C chemical shifts of the α carbon atoms (for the α methyne groups of the unknown *Z* isomer of **6b** we would have expected δC values of 38–40 ppm and ca. 45 ppm, respectively,



Scheme 3. Reactions of erythromycin A and clarithromycin oximes. Relevant chemical shifts in $CDCl_3$ are given for the erythromycin series. For clarithromycins the chemical shifts are very close to those indicated.

according to the trends mentioned above); (ii) the chemical shift of the 10-Me group (equatorial), which is almost identical for (*E*)-**6a** and (*E*)-**6b**, as it was the case for the equatorial Me of (*E*)-**5a** and (*E*)-**5b**, whereas the congested 10-Me of (*Z*)-**6a** appears at 10.8 ppm; and (iii) the δH values for equatorial hydrogens, which show a parallelism with those observed in the case of (*E*)-**5a** and (*E*)-**5b** (see above). We should remark that no signals attributable to sulfenylimine *Z* were detected in the crude product or in equilibrium with the *E* isomer. Apparently, the less stable *Z* isomer is in the case of **6a** much more disfavoured than in the case of **5**,[23] a fact that can be accounted for on steric grounds and by the lack of an alternative chair conformation because of the restrictions imposed by the macrolide ring.

Clarithromycin oxime,[24] when treated with an excess of Bu_3P and PhSSPh (1:4:8 ratio as above) in 1:1 THF–dioxane (to solubilise the oxime), gave a high percentage of conversion to (*E*)-**7b**,[25] even though as in the previous case after separation by column chromatography on alumina we obtained only a 48% yield (and later a 25% yield of imine **7c** was eluted). Again, only the more stable *E* isomer was formed or detected by NMR (see Scheme 3).

Having established that, in all the reactions of **1a**–**7a** with Bu_3P and PhSSPh, the 1:*n*:2*n* ratio favours the formation of the *N*-SPh derivatives (**1b**–**7b**), we focused our attention on finding suitable conditions for obtaining the ketimines as major compounds. It was achieved with a more active reagent combination.[1] Thus, imine **1c** was the unique cyclopentadecanone derivative observed by carrying out the reaction of oxime **1a** with Me_3P (2.4 equiv) and PySeSePy (1.2 equiv) in a NMR tube in $CDCl_3$ (confirming the data shown in Scheme 1). The success of this method is based on the fact that in a preceding work[1] we had not observed or detected any *N*-SePy intermediate. Our working hypothesis was that this intermediate and/or a previous one are very quickly cleaved by the phosphine present in the medium. Isolation of **1c** as a pure compound was not possible due to its easy hydrolysis, but the sample was stable protecting it from the moisture. This imine can be trapped,[4] but we preferred to convert it to its parent ketone **1d** by pouring the crude product into aqueous ethanol. The hydrolysis was instantaneous and complete.

When oximes (*E*)-**6a** and (*E*)-**7a** were independently treated with PySeSePy (4 equiv) and a larger excess of Me_3P or Bu_3P (8 equiv) for 10 min at 0 °C, only imines **6c** and **7c** were observed (MALDI, NMR). They were isolated, after a cold aqueous workup at pH 10 and extraction with dichloromethane, in ca. 80% yields.[26] Thus, in these exceptional cases, owing to the relatively high kinetic stability of these macrocyclic, congested imines, their isolation and full characterisation is feasible. To hydrolyse these imines to the parent macrolides we dissolved them into aqueous ethanol and added some drops of dilute HCl until pH 5–6.

In conclusion, under appropriate conditions, one can stop or drive the conversion of ketoximes to *N*-phenylsulfenyl derivatives (substrate/Bu_3P/PhSSPh in the 1:*n*:2*n* ratio), imines (substrate/Me_3P/PySeSePy in the 1:2*n*:*n* ratio) or ketones (1:2*n*:*n*, followed by addition of water). Applications of these reactions to the protection and modification of erythromycin-related antibiotics are in progress.

Acknowledgements

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5. The reactive species may be a charge transfer complex (P–S interaction), and/or a P-tetracoordinated ionic species, $R_3P^+SPh^-SPh$, and/or a P-pentacoordinated species, $R_3P(SPh)_2$, depending on the medium polarity, temperature, etc. For an entry to the subject, see: Godfrey, S. M.; Kelly, D. G.; McAuliffe, C. A.; Mackie, A. G.; Pritchard, R. G.; Watson, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1163. Generally speaking, in R_3P/XY equilibrium mixtures several P-tetravalent species ($R_3PX^+Y^-$ and $R_3PY^+X^-$, but also $R_3PX^+X^-$ and $R_3PY^+Y^-$, arising from exchange reactions) and/or P-pentavalent species (R_3PXY, as well as R_3PXX and R_3PYY) may be present.
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9. *N*-(Phenylsulfenyl)cyclopentadecanimine (**1b**): colourless oil; R_f 0.75 (50:50 EtOAc/hexane); IR (film) 1711, 1610, 1584, 1478, 1441 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (pseudo dd, $J = 7.2$ Hz, $J = 1.2$ Hz, 2H), 7.33 (pseudo t, $J \approx 7.2$ Hz, 2H), 7.19 (tt, $J = 7.2$ Hz,

$J = 1.2$ Hz, 1H), 2.45 (t, $J = 7.6$ Hz, 2H), 2.41 (t, $J = 7.6$ Hz, 2H), 1.76–1.64 (m, 4H), 1.48–1.30 (m, 20H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.8, 139.6, 128.7, 125.5, 124.8, 40.3, 36.3, 27.8, 27.3, 26.7, 26.5, 26.4, 26.3, 26.2, 26.1, 25.0, 23.8; MS (CI) m/z 334 ($M+3^+$, 7), 333 ($M+2^+$, 25) 332 ($M+1^+$, 100); HRMS (+FAB) calcd for $[M+H]^+$ $C_{21}H_{34}NS$ 332.2412, found 332.2421.

10. The quick cleavage of the N–S bond by phosphines and water was confirmed by treating a pure sample of sulfenimine **1b** with an equivalent amount of Me_3P in THF–H_2O at rt (Ref. 8), in agreement with the results of Lukin and Narayanan with a relevant erythromycin derivative (Ref. 7). Ketone **1d** was detected immediately by TLC and was quantitatively isolated after half an hour. Hydrolysis of **1b** in THF–H_2O, in the absence of the phosphine, either in acidic media or in the presence of cyanide ion, required an overnight stirring (Ref. 8). Phenylsulfenylimines are much more resistant to conventional hydrolyses than the corresponding imines. See: Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809.
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12. The NMR assignments shown were corroborated by ^{1}H–^{13}C 2D experiments (HSQC).
13. No reaction occurs with Ph_3P under the same conditions.
14. The *E–Z* isomerisation energy barriers of *N*-sulfenyl ketimines are, in general, relatively low (ca. 15–20 kcal/mol, coalescence temperatures around 50–70 °C). See: (a) Brown, C.; Grayson, B. T.; Hudson, R. F. *Tetrahedron Lett.* **1970**, 4925; (b) Davis, F. A.; Slegeir, W. A. R.; Kaminski, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 634; (c) Brown, C.; Hudson, R. F.; Grayson, B. T. *J. Chem. Soc., Chem. Commun.* **1978**, 156; Also see: (d) Bharatam, P. V.; Amita; Kaur, D. *J. Phys. Org. Chem.* **2003**, *16*, 183.
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23. It would be interesting to investigate whether both pathways to (*E*)-**6b** from (*E*)-**6a**, summarised by means of arrows at the top of Scheme 3, are involved or not. In other words, if (*Z*)-**6b** is formed first and it immediately isomerises to (*E*)-**6b**, or if (*E*)-**6b** comes mainly from the small percentage of (*Z*)-**6a** that may be in equilibrium with (*E*)-**6a** under the reaction conditions. However, such a study is outside the scope of this communication.
24. The samples we have utilised were 90:10 *E*/*Z*. cf. Waddell, S. T.; Santorelli, G. M.; Blizzard, T. A.; Graham, A.; Occi, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1321.
25. Spectral data of (*E*)-**7b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (pseudo dd, $J = 8.4$ Hz $J = 1.2$ Hz, 2H, H_o), 7.34 (pseudo dd, $J \approx 8.4$ Hz, $J \approx 7.2$ Hz, 2H, H_m), 7.18 (tt, $J = 7.2$ Hz, $J = 1.4$ Hz, 1H, H_p), 5.11 (dd, $J = 11.1$ Hz, $J = 2.1$ Hz, 1H, H13), 4.94 (d, $J = 4.5$ Hz, 1H, H1″), 4.91 (s, 1H, 11-OH), 4.49 (d, $J = 7.2$ Hz, 1H, H1′), 4.04 (dq, $J = 9.0$ Hz, $J = 6.5$ Hz, 1H, H5″), 3.78–3.71 (m, 3H, H3, H5, H11), 3.58–3.44 (m, 1H, H5′), 3.33 (s, 3H, 3″-OMe), 3.30 (d, $J = 11.7$ Hz, 1H, H2′), 3.18 (s, 3H, 6-OMe), 3.24–3.10 (m, 1H, H8), 3.02 (t, $J = 9.6$ Hz, 1H, H4″), 3.00–2.86 (m, 1H, H2), 2.77 (q, $J = 7.2$ Hz, 1H, H10), 2.48–2.40 (m, 1H, H3′), 2.36 (d, $J = 15.3$ Hz, 1H, H2″b), 2.29 (s, 6H, NMe_2), 2.18 (d, $J = 8.7$ Hz, 1H, 4″-OH), 2.03–1.84 (m, 2H, H14b, H4), 1.80–1.41 (m, 8H, 6-Me, H4′b, H7a, H7b, H2″a, H14a), 1.30 (d, $J = 6.3$ Hz, 3H, 5″-Me), 1.25–1.19 (m, 13H, 10-Me, 2-Me, 5′-Me, 3″-Me, H4′a), 1.13 (s, 3H, 12-Me), 1.11 (d, $J = 7.5$ Hz, 4-Me), 1.09 (d, $J = 6.6$ Hz, 3H, 8-Me), 0.83 (t, $J = 7.5$ Hz, 3H, H15) (assignments confirmed by COSY and HSQC); ^{13}C NMR ($CDCl_3$, 75.3 MHz) δ 182.2 (C9), 175.2 (C1), 138.9 (C_{ipso}), 128.9 (C_m), 126.0 (C_p), 125.5 (C_o), 102.5 (C1′), 96.1 (C1″), 80.1 (C5), 78.6 (C3), 78.3 (C4″), 77.9 (C6), 76.7 (C13), 74.1 (C12), 72.7 (C3″), 71.0 (C2′), 70.2 (C11), 68.6 (C5′), 65.7 (C5″), 65.5 (C3′), 52.1 (6-OMe), 49.4 (3″-OMe), 44.9 (C2), 40.3 (NMe_2), 38.5 (C4), 38.3 (C7), 37.8 (C8), 36.3 (C10), 34.9 (C2″), 28.6 (C4′), 21.5 (5′-Me), 21.5 (3″-Me), 21.1 (C14), 20.5 (6-Me), 18.6 (5″-Me), 18.6 (8-Me), 16.1 (2-Me or 10-Me), 15.9 (12-Me), 15.0 (10-Me or 2-Me), 10.6 (C15), 9.2 (4-Me); MS (MALDI) m/z 855.6 ($M+1^+$).
26. Compounds **6c** and **7c** thus obtained were identical (TLC, NMR) to those prepared by us from the $TiCl_3$/HCl/NH_4OAc reduction of (*E*)-**6a** and (*E*)-**7a**, respectively. See: Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, *12*, 195.