Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1694–1697
Tetrahedron Letters

# Hydrazine sulphate: a cheap and efficient catalyst for the regioselective ring-opening of epoxides. A metal-free procedure for the preparation of β-alkoxy alcohols

Alcino J. L. Leitão [a], Jorge A. R. Salvador [b,*], Rui M. A. Pinto [b], M. Luísa Sá e Melo [a]

[a] *Centro de Estudos Farmacêuticos, Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, Coimbra 3000-295, Portugal*
[b] *Laboratório de Química Farmacêutica, Faculdade de Farmácia, Universidade de Coimbra, Coimbra 3000-295, Portugal*

Received 5 December 2007; accepted 21 December 2007
Available online 8 January 2008

**Abstract**

An efficient and general procedure for the regioselective ring opening of epoxides with alcohols to afford the corresponding β-alkoxy alcohols, using hydrazine sulphate as catalyst, is described. This new metal-free process was found to be highly versatile allowing the use of primary, secondary and tertiary alcohols as nucleophiles and a large variety of epoxides, including 5α,6α-, 5β,6β- and 2α,3α-epoxy-steroids, as substrates.


*Keywords:* Hydrazine sulphate; Metal-free catalysis; Epoxides; Steroids; β-Alkoxy alcohols

Ring opening of epoxides with nucleophilic reagents is an useful tool for the preparation of several 1,2-disubstituted products.[1] β-Alkoxy alcohols are important intermediates for the preparation of α-alkoxy ketones and α-alkoxy acids as well as for the synthesis of compounds with pharmaceutical interest.[2,3]

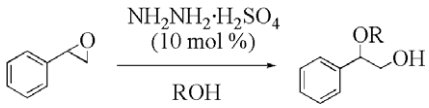
The most common and simple protocol for the synthesis of β-alkoxy alcohols is the ring opening of epoxides with an appropriate alcohol under strongly acidic[4] or basic[5] conditions. Commercially available Woelm 200 neutral chromatographic alumina,[6] Nafion-H, a perfluorinated sulfonic acid resine[7] and organotin phosphate condensates[8] have been applied as heterogeneous reagents for the alcoholysis of epoxides. However, the fact that these reagents have to be prepared prior to their use plus the large amounts needed to perform these reactions led to the development of more convenient processes. The use of one-electron transfer catalysts, such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[9] tetracyanoethylene (TCNE)[10] and ceric(IV) ammonium nitrate (CAN)[11] as well as electron deficient metalloporphyrins[12] has been reported for this reaction. Alternatively, procedures that use metal salts in stoichiometric amounts[13] or Lewis acid catalysts under homogeneous[14] or heterogeneous conditions[15] have also been described. Quite recently, heteropolyoxometalates[16] were introduced as heterogeneous catalysts for this reaction and Robinson and co-workers reported the alcoholysis of epoxides promoted by a mesoporous aluminosilicate catalyst.[17] Despite the fact that these methods generally lead to high yields with good regioselectivity, the handling of toxic and/or expensive reagents, intolerance to highly sensitive groups, unwanted by-products and relatively limited scope of the application of some of the methods restricts their widespread applicability.

The development of metal-free synthetic methods is an area of great interest. This approach avoids the use of toxic and expensive metals and is particularly attractive for the preparation of compounds that do not

* Corresponding author. Tel.: +351 239 859900; fax: +351 239 827126.
*E-mail address:* salvador@ci.uc.pt (J. A. R. Salvador).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.121

Table 1
Hydrazine sulphate-catalyzed alcoholysis of styrene oxide[a]




**1** **1a-1e**

| Entry | R | Temp (°C) | Time (h) | Product[b] | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 | Me[d] | rt | 90 | **1a** | Traces |
| 2 | Me | rt | 3 | **1a** | 87 |
| 3 | Et | rt | 5 | **1b** | 94 |
| 4 | Et[e] | rt | 5 | **1b** | 96 |
| 5 | Me | 50 | 0.25 | **1a** | 92 |
| 6 | Et | 50 | 0.5 | **1b** | 96 |
| 7 | *n*-Pr | 50 | 1 | **1c** | 93 |
| 8 | *i*-Pr | 50 | 4 | **1d** | 86 |
| 9 | *t*-Bu | 50 | 4 | **1e** | 63 |

[a] Reaction conditions: 0.2 M solution of styrene oxide in the appropriated alcohol; 10 mol % of catalyst.
[b] All products **1a**–**1e** gave satisfactory analytical data according to the literature.[14g,21]
[c] Isolated yield after flash column chromatography.
[d] Reaction performed in the absence of $NH_2NH_2{\cdot}H_2SO_4$.
[e] Reaction performed using the recovered catalyst after filtration.

tolerate metal contamination, such as pharmaceutical products.[18]

As part of our ongoing project on the application of hydrazine and hydrazine salts as non-metallic reagents in organic chemistry,[19] we report in this Letter the use of hydrazine sulphate[20] as an efficient catalyst for the synthesis of β-alkoxy alcohols.

Our initial studies showed that $NH_2NH_2{\cdot}H_2SO_4$ is an adequate catalyst for the ring opening of styrene oxide **1** with primary, secondary and tertiary alcohols (Table 1).

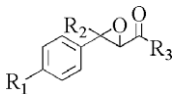
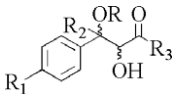
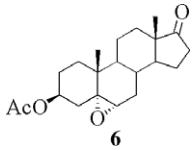
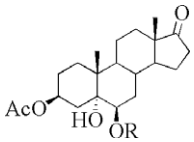
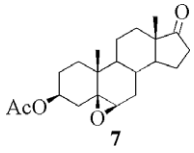
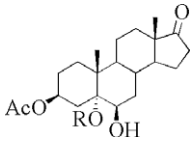
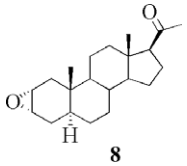
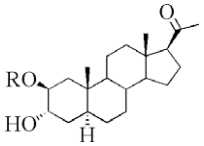
No significant reaction occurred in the absence of $NH_2NH_2{\cdot}H_2SO_4$ (Table 1, entry 1). The reaction was initially screened using stoichiometric amounts of $NH_2NH_2{\cdot}H_2SO_4$ but it rapidly became evident that the reaction proceeds well using 10 mol % of catalyst at rt (Table 1, entries 2 and 3). The ring opening of styrene oxide **1** occurred at the benzylic position, as expected, and the β-alkoxy alcohols **1a** and **1b** were obtained on the reactions performed with MeOH and EtOH, in 87 and 94% yield, respectively (Table 1, entries 2 and 3). Due to its very low solubility in alcohols, $NH_2NH_2{\cdot}H_2SO_4$ can be almost quantitatively recovered and reused without the need for further activation or loss of activity (Table 1, entry 4). In fact, from a practical point of view, not only is the possibility of recovery and reuse noteworthy, but also the work-up procedure becomes easier.[22] The ring opening of styrene oxide **1** with MeOH and EtOH was then performed at 50 °C and significantly shorter reaction times were observed (Table 1, entries 5 and 6). Thus, we considered the use of this temperature for studying the process. The hydrazine sulphate-catalyzed ring opening of styrene oxide **1** with *n*-PrOH, *i*-PrOH and *t*-BuOH afforded the corresponding β-alkoxy alcohols **1c**–**1e**, in 63–93% yield (Table 1, entries 7–9).

The success of this first set of experiments using $NH_2NH_2{\cdot}H_2SO_4$ (10 mol %) as a catalyst encouraged us to enlarge the scope of the reaction to other epoxides. Thus, the alcoholysis of α-epoxyketone **2**, the 3-phenylglycidate derivatives **3**–**5** and epoxysteroids **6**–**8** with MeOH and EtOH afforded the corresponding β-alkoxy alcohols **2a**–**8a** in high yields (Table 2). For substrates **2**–**5**, the reactions were also regioselective with the nucleophilic attack occurring invariably at the benzylic position (Table 2, entries 1–8). The reactions performed using MeOH (Table 2, entries 1, 3, 5 and 7) gave shorter reaction times than the ones with EtOH (Table 2, entries 2, 3, 6 and 8). The β-alkoxy alcohols **2a**–**5b** were obtained as mixtures of *anti*- and *syn*-isomers in a ratio ranging from 1:1 to 4:1 (Table 2, entries 1–8).

The hydrazine sulphate-catalyzed alcoholysis of the epoxysteroids **6**–**8** was not only regioselective but also stereoselective as result of the trans-diaxial ring opening of these substrates (Table 2, entries 9–13). Treatment of 5α,6α-epoxy-17-oxoandrostan-3β-yl acetate **6** with $NH_2NH_2{\cdot}H_2SO_4$ (10 mol %) in MeOH or EtOH afforded the corresponding 5α-hydroxy-6β-alkoxy derivatives **6a** and **6b** in 75% and 70% yield, respectively (Table 2, entries 9 and 10), whereas 5β,6β-epoxide **7** gave the 5α-alkoxy-6β-hydroxy products **7a** and **7b**, in 81% and 80% yield, respectively (Table 2, entries 11 and 12). It is important to note that under these reaction conditions the acetoxy functions remained intact. The structure and stereochemistry of the new steroid compounds **6b** and **7b** were established based on the related literature[23] and analysis of NMR data. For both compounds **6b** and **7b**, the multiplicity of the 3α-H signal (a broad multiplet), which indicates a trans-fused (5α,10β)-steroid structure, and the coupling pattern observed for 6-H (triplet, $J = 2.6$ and $J = 2.8$ Hz, respectively), which suggests equatorial–equatorial and equatorial–axial couplings consistent with a 6β-substitution, confirm the trans-diaxial nature of the epoxide ring opening. For the 5α-hydroxy-6β-ethoxy derivative **6b**, the chemical shift value of the 6α-H (3.08 ppm) is consistent with a 6β-OEt group whilst the value of 3.95 ppm for the 6α-H of the 5α-ethoxy-6β-hydroxy product **7b** is in accordance with a 6β-OH function. The hydrazine sulphate-catalyzed ring opening of 2α,3α-epoxy-5α-pregnan-20-one **8** with EtOH resulted in the formation of the 2β-ethoxy-3α-hydroxy steroid **8a**, in 90% yield, after 30 h of reaction (Table 2, entry 13).

In conclusion, we developed an efficient metal-free process for the ring opening of epoxides, including several epoxysteroids, with a wide set of representative alcohols. This method takes place under relatively mild conditions and relies simply on the use of catalytic amounts of the cheap and commercially available hydrazine sulphate. Other important features such as the stability of ester groups, high yields, easy work-up and high regioselectivity make this new process an attractive alternative to current methodologies.

Table 2
Reaction of epoxides with alcohols (ROH) using hydrazine sulphate as a catalyst[a]

| Entry | Epoxide | R–OH | Time (h) | Product[b]/yield[c] (%) |
|---|---|---|---|---|
| |  | | |  |
| 1 | **2**[d]: $R_1 = R_2 = H$; $R_3 = Ph$ | R = Me | 5 | **2a**/93 (*anti*/*syn* = 3.2/1) |
| 2 | **2**[d]: $R_1 = R_2 = H$; $R_3 = Ph$ | R = Et | 24 | **2b**/93 (*anti*/*syn* = 5.7/1) |
| 3 | **3**[d]: $R_1 = R_3 = OMe$; $R_2 = H$ | R = Me | 1 | **3a**/91 (*anti*/*syn* = 2/1) |
| 4 | **3**[d]: $R_1 = R_3 = OMe$; $R_2 = H$ | R = Et | 12 | **3b**/90 (*anti*/*syn* = 1.6/1) |
| 5 | **4**[e]: $R_1 = R_2 = H$; $R_3 = OEt$ | R = Me | 16 | **4a**/87 (*anti*/*syn* = 3.8/1) |
| 6 | **4**[e]: $R_1 = R_2 = H$; $R_3 = OEt$ | R = Et | 48 | **4b**/85 (*anti*/*syn* = 4/1) |
| 7 | **5**[e]: $R_1 = H$; $R_2 = Me$; $R_3 = OEt$ | R = Me | 20 | **5a**/91 (*anti*/*syn* = 1/1) |
| 8 | **5**[e]: $R_1 = H$; $R_2 = Me$; $R_3 = OEt$ | R = Et | 48 | **5b**/90 (*anti*/*syn* = 1/1) |
| |  **6** | | |  |
| 9 | | R = Me | 24 | **6a**/75 |
| 10 | | R = Et | 30 | **6b**/70 |
| |  **7** | | |  |
| 11 | | R = Me | 10 | **7a**/81 |
| 12 | | R = Et | 36 | **7b**/80 |
| |  **8** | | |  |
| 13 | | R = Et | 30 | **8a**/90 |

[a] Reaction performed at 50 °C using 10 mol % of $NH_2NH_2{\cdot}H_2SO_4$.
[b] Analytical data for compounds **2a**,[24a] **3a**,[24b] **4a**,[24c] **4b**,[24c] **5a**,[24d] **6a**,[23] **7a**[23] and **8a**[24e] are in accordance with the literature. For compounds **2b**, **3b**, **5b**, **6b** and **7b** see selected analytical data.[25]
[c] Isolated yield after flash column chromatography.
[d] The racemic trans-isomer was used.
[e] A mixture of cis- and trans-isomers was used.

## Acknowledgements

J.A.R.S. thanks Universidade de Coimbra for financial support. M.L.S.M. and A.J.L.L. thank Fundação para a Ciência e Tecnologia (FCT) through POCI (FEDER). R.M.A.P. also thanks FCT for financial support (SFRH/BD/18013/2004).

## References and notes

1. Smith, J. G. *Synthesis* **1984**, 629–656.
2. Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.
3. (a) Jones, R. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 1144–1146; (b) Jaramillo, C.; Chiara, J. L.; Martinlomas, M. *J. Org. Chem.* **1994**, *59*, 3135–3141; (c) Stead, P.; Marley, H.; Mahmoudian, M.; Webb, G.; Noble, D.; Ip, Y. T.; Piga, E.; Rossi, T.; Roberts, S.; Dawson, M. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2247–2250.
4. Battistini, C.; Crotti, P.; Damiani, D.; Macchia, F. *J. Org. Chem.* **1979**, *44*, 1643–1647.
5. Mall, T.; Stamm, H. *J. Org. Chem.* **1987**, *52*, 4812–4814.
6. Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208–8214.
7. Olah, G. A.; Fung, A. P.; Meidar, D. *Synthesis* **1981**, 280–282.
8. Otera, J.; Niibo, Y.; Tatsumi, N.; Nozaki, H. *J. Org. Chem.* **1988**, *53*, 275–278.
9. Iranpoor, N.; Baltork, I. M. *Tetrahedron Lett.* **1990**, *31*, 735–738.
10. Masaki, Y.; Miura, T.; Ochiai, M. *Synlett* **1993**, 847–849.
11. Iranpoor, N.; Baltork, I. M. *Synth. Commun.* **1990**, *20*, 2789–2797.
12. Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. *Tetrahedron* **2004**, *60*, 6105–6111.
13. Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett* **1992**, 673–676.
14. (a) Moberg, C.; Rakos, L.; Tottie, L. *Tetrahedron Lett.* **1992**, *33*, 2191–2194; (b) Iranpoor, N.; Salehi, P. *Synthesis* **1994**, 1152–1154; (c) Baltork, I. M.; Tangestaninejad, S.; Aliyan, H.; Mirkhani, V. *Synth. Commun.* **2000**, *30*, 2365–2374; (d) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2002**, *4*, 2817–2819; (e) Chandrasekhar, S.; Reddy, C. R.; Babu, B. N.; Chandrashekar, G.

*Tetrahedron Lett.* **2002**, *43*, 3801–3803; (f) Kantam, M. L.; Jeyalakshmi, K. A. K.; Likhar, P. R. *Catal. Lett.* **2003**, *89*, 95–97; (g) Kim, B. H.; Piao, F. Y.; Lee, E. J.; Kim, J. S.; Jun, Y. M.; Lee, B. M. *Bull. Korean Chem. Soc.* **2004**, *25*, 881–888.

15. (a) Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* **1996**, 1473–1476; (b) Yarapathi, R. V.; Reddy, S. M.; Tammishetti, S. *React. Funct. Polym.* **2005**, *64*, 157–161.
16. (a) Mirkhani, V.; Tangestaninejad, S.; Yadollahi, B.; Alipanah, L. *Tetrahedron* **2003**, *59*, 8213–8218; (b) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A.; Makarem, S. *J. Mol. Catal. A: Chem.* **2006**, *250*, 237–242.
17. Robinson, M. W. C.; Buckle, R.; Mabbett, I.; Grant, G. M.; Graham, A. E. *Tetrahedron Lett.* **2007**, *48*, 4723–4725.
18. *Guideline on the specification limits for residues of metal catalysts*, European Medicines Agency, Pre-authorisation Evaluation of Medicines for Human Use; London, January **2007**; Doc. Ref. CPMP/SWP/QWP/4446/00; http://www.emea.europa.eu/.
19. Salvador, J. A. R.; Leitão, A. J. L.; Melo, M. L. S.; Hanson, J. R. *Tetrahedron Lett.* **2005**, *46*, 1067–1070.
20. Despite some concern related to its toxicity, hydrazine sulphate has been used in clinical practice for the treatment of cachexia associated with cancer. See: Ernst, E.; Cassileth, B. R. *Eur. J. Cancer* **1999**, *35*, 1608–1613.
21. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1113–1121.
22. *Typical procedure*: to a solution of 5β,6β-epoxy-17-oxoandrostan-3β-yl acetate **7** (346.5 mg, 1.0 mmol) in EtOH (20 mL), $NH_2NH_2{\cdot}H_2SO_4$ (13 mg, 0.1 mmol) was added. After 30 h under magnetic stirring at 50 °C the reaction was completed as verified by TLC control. The reaction mixture was filtered, the catalyst was recovered (11 mg, 85%) and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to afford 5α-ethoxy-6β-hydroxy-17-oxoandrostan-3β-yl acetate **7b** as a white solid (314.0 mg, 80% yield).
23. Boynton, J. A.; Hanson, J. R.; Uyanik, C. *J. Chem. Res., Synop.* **1995**, 334–335.
24. (a) Plietker, B. *Eur. J. Org. Chem.* **2005**, 1919–1929; (b) Hashiyama, T.; Watanabe, A.; Inoue, H.; Konda, M.; Takeda, M.; Murata, S.; Nagao, T. *Chem. Pharm. Bull.* **1985**, *33*, 634–641; (c) Chai, W.; Takeda, A.; Hara, M.; Ji, S. J.; Horiuchi, C. A. *Tetrahedron* **2005**, *61*, 2453–2463; (d) Vanchung, V.; Tokuda, M.; Suzuki, A.; Itoh, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 341–342; (e) Phillipps, G. H.; Newall, C. E.; Ayres, B. E. US Patent 3,952,031, 1976.
25. *Selected analytical data*: Compound **2b**: Colourless liquid; IR (film) 3474, 3062, 2976, 1682, 1598, 1402, 1098 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.05 (t, $J = 7.0$ Hz, 3H), 3.24–3.41 (m, 2H), 3.89 (s, 1H); 4.55 (d, $J = 4.8$ Hz, 1H), 5.33 (d, $J = 4.8$ Hz, 1H), 7.15–7.87 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.8, 64.7, 76.0, 83.5, 127.3, 127.9, 128.3, 128.6, 133.5, 135.1, 137.1, 199.9.
Compound **3b**: Colourless liquid; IR (film) 3490, 2973, 1745, 1612, 1440, 1250, 1094 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (t, $J = 7.1$ Hz, 3H), 2.48 (s, 1H), 3.29–3.51 (m, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 4.23 (d, $J = 3.4$ Hz, 1H), 4.62 (d, $J = 3.4$ Hz, 1H), 6.90 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.8$ Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 15.0, 52.4, 55.2, 64.6, 75.3, 81.2, 113.7, 128.4, 129.7, 159.4, 172.6.
Compound **5b** (*anti*/*syn* = 1/1): Colourless liquid; IR (film) 3504, 3059, 2979, 1732, 1447, 1391, 1105; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (t, $J = 7.1$ Hz, 3H), 1.20 (t, $J = 7.0$ Hz, 3H), 1.69 (s, 3H), 2.70 (s, 1H), 3.16–3.30 (m, 1H), 3.42–3.47 (m, 1H), 3.96–4.08 (m, 2H), 4.16 (s, 1H), 7.30–7.36 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.8, 13.9, 15.5, 18.7, 20.1, 58.1, 58.3, 60.9, 61.0, 78.4, 78.5, 80.4, 80.6, 126.5, 126.9, 127.4, 127.6, 128.0, 128.1, 140.9, 141.3, 171.6, 172.0.
Compound **6b**: mp 179–181 °C (*n*-hexane/acetone); IR (film) 3477, 2939, 1735, 1026 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.88 (s, 3H, 18-$CH_3$), 1.14 (s, 3H, 19-$CH_3$), 1.17 (t, $J = 6.8$ Hz, 3H, $OCH_2CH_3$), 2.04 (s, 3H, $CH_3COO$), 3.08 (t, $J = 2.6$ Hz, 1H, 6α-H), 3.29 and 3.59 (2m, 2H, $OCH_2CH_3$), 5.14 (m, 1H, 3α-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 65.5 ($OCH_2CH_3$); 71.1 (C-3); 75.9 (C-5); 83.2 (C-6); 170.9 ($CH_3COO$); 221.3 (C-17); EI-MS *m*/*z* (%): 392(14) $M^+$, 314 (26), 270 (100), 232 (42), 179 (82), 151 (29), 91 (36), 79 (40).
Compound **7b**: mp 202–204 °C (acetone); IR (film) 3523, 2941, 1731, 1023 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.88 (s, 3H, 18-$CH_3$), 1.16 (t, $J = 6.9$ Hz, 3H, $OCH_2CH_3$), 1.22 (s, 3H, 19-$CH_3$), 2.03 (s, 3H, $CH_3COO$), 3.29 and 3.54 (2m, 2H, $OCH_2CH_3$), 3.95 (t, $J = 2.8$ Hz, 1H, 6α-H), 4.86 (m, 1H, 3α-H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 55.2 ($OCH_2CH_3$); 69.9 (C-6); 71.1 (C-3); 78.5 (C-5); 170.8 ($CH_3COO$); 221.4 (C-17); EI-MS *m*/*z* (%): 392(6) $M^+$, 346 (8), 299 (7), 286 (90), 268 (100), 253 (26), 123 (31), 91 (41).