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An approach to oxazolidin-2-ones from the Baylis–Hillman adducts. Formal synthesis of a chloramphenicol derivative

Fernando Coelho* and Rodrigo C. Rossi

DQO, IQ/Unicamp, PO Box 6154, 13083-970 Campinas, São Paulo, Brazil

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Abstract—In this communication we describe a straightforward and diastereoselective approach to prepare functionalised oxazolidin-2-ones from Baylis–Hillman adducts. A stereoselective synthesis of a highly substituted vicinal aminoalcohol and a formal synthesis of a chloramphenicol derivative are also described. © 2002 Elsevier Science Ltd. All rights reserved.

Oxazolidin-2-ones are a very interesting class of compounds due to their various pharmacological effects.[1] They are described as potential neuroleptics with a high affinity for sigma receptors,[2] as psychotropics,[3] as antiallergy agents,[4] as antibacterials and antibiotics,[5] as intermediates in the syntheses of renin inhibitors,[6] β-lactams and macrolide antibiotics,[7] immunosupressants,[8] and in other applications, mainly in synthetic organic chemistry as chiral auxiliaries.[9] Particularly as synthetic antibacterials, this class of compounds exhibits activity against many antibiotic-resistant strains of Gram-positive bacteria.[10,11] They represent the only completely new class of antibiotics licensed over the past 30 years.[12]

Due to these important biological effects and synthetic uses, several methods of preparing oxazolidin-2-ones are described in the literature.[13] Normally, these compounds can be obtained from α,β-difunctional substrates such as β-aminoalcohols, oxiranes and aziridines, in the presence of phosgene,[14] carbonate,[13] isocyanate,[1,15] or carbon dioxide.[16,17] Strategies based on the utilisation of solid state chemistry[1,10,18] were recently described as a tool for their preparation.

2-Oxazolidin-2-ones can be easily interconverted into aminoalcohols and vice-versa. Thus, an approach directed towards the preparation of highly functionalised 2-oxazolidin-2-ones could also allow access to aminoalcohols with varied substitution patterns. On the other hand, vicinal aminoalcohols exhibit interesting biological activities. For example, chloramphenicol and derivatives (thiamphenicol and fluoramphenicol) are aminoalcohols showing therapeutical use as broad-spectrum antibiotics.

In an ongoing research program focused on the synthesis of new compounds to be used as candidates for biological screening as antibiotics, it was necessary to prepare some modified oxazolidin-2-ones, whose structural core is depicted in Fig. 1.

Our main interest was focused on evaluating the effect of substitution at position 5 on membrane transportation and consequently on biological activity as antibiotic agents. Initially we were interested to check the biological profile of oxazolidin-2-ones with aromatic substituents in that position, with electron donor groups on the ring.

To accomplish our objective we decided to take advantage of the great potential synthetic versatility exhibited by a α-methylene-β-hydroxy ester. This class of compounds could be readily prepared through a Baylis–Hillman reaction.[19] This reaction is a very interesting

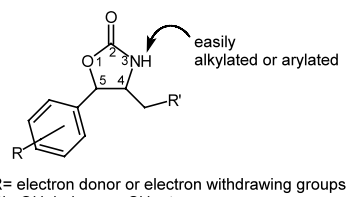

Figure 1. Structural core of required oxazolidin-2-ones.

Keywords: oxazolidin-2-one; Baylis–Hillman reaction; chloramphenicol derivative.

* Corresponding author. Tel.: 55 19 3788-3085; fax: 55 19 3788-3023; e-mail: coelho@iqm.unicamp.br

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way to form a new C–C σ bond and can be broadly defined as a coupling reaction between an aldehyde and an acrylate derivative in the presence of a tertiary amine or phosphine.

Owing to the high degree of functionality, these derivatives are predisposed to serve as starting materials for our purposes. In this communication, we describe preliminary results concerning a new route to functionalised oxazolidin-2-ones using Baylis–Hillman adducts as substrates.

From our point of view, the oxazolidin-2-one (**1**) we needed could be synthesised according to the retrosynthetic analysis shown in Scheme 1.
Thus, **1** could be obtained through an intramolecular reaction involving the regioselective attack of the secondary hydroxyl group on isocyanate **2**. To avoid any competition between the two hydroxyl groups, their chemical reactivity could be modulated through the correct manipulation of the protective groups. Isocyanate **2** could be secured from hydroxyacid **3**, using a stereospecific Curtius rearrangement. To prepare **3**, we should explore the chemical reactivity of the double bond presented in the structure of allyl alcohol **4**, using a hydroboration reaction followed by the oxidation of the primary alcohol to the carboxylic acid. Most probably, the diastereoselectivity of this sequence could be controlled in the hydroboration step. Previous results from our laboratory point in this direction.[20] Finally, access to allyl alcohol **4** could be readily guaranteed from the Baylis–Hillman adduct **5**, using a chemoselective reduction reaction.

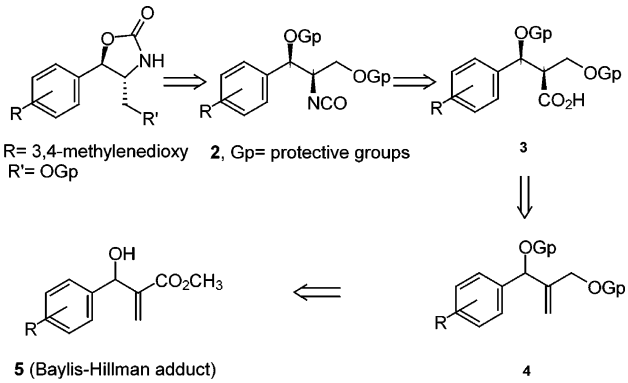
Depending on the success attained with this sequence, hydrolysis of oxazolidin-2-one (**1**), under controlled conditions, allowed the preparation of a vicinal aminoalcohol, which could be used as a substrate for the synthesis of a chloramphenicol derivative.

Our synthesis started with the Baylis–Hillman reaction between piperonal and methyl acrylate to furnish **5**, in 55% yield (73% yield based on recovered aldehyde).[21] Protection of the secondary hydroxyl group as TIPS ether, followed by chemoselective reduction with DIBAL-H, at −78°C, in dichloromethane gave the allyl alcohol **6**. The primary alcohol was then protected as TBS ether to provide allyl alcohol **4**, in 86% overall yield (Scheme 2).

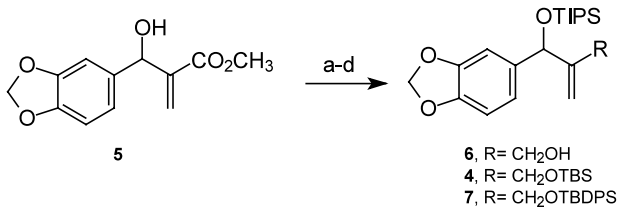
The allyl alcohol **4** was then treated with $BH_3{\cdot}S(CH_3)_2$ in THF to give the triol **8**, as a mixture of diastereomers (Scheme 3), in 85% yield. Unfortunately, in this case no diastereoselectivity was observed.

Intrigued by the lack of diastereoselection observed, we decided to check the eventual influence of steric hindrance on the diastereoselectivity of the hydroboration reaction. Thus, we prepared the allyl alcohol **7**, in which the protective group of the primary hydroxyl group was replaced by a bulkier silyl ether (*t*-butyldiphenyl, Scheme 2). In addition, 9-BBN was used with both alcohols (**4** and **7**) and the results compared with those obtained with $BH_3{\cdot}S(CH_3)_2$ (Scheme 3). As expected, when we employed a bulky borane we observed a moderate diastereoselection on the hydroboration of the allyl alcohol **4**. However, the degree of diastereoselectivity was dramatically increased when a bulky borane was conjugated with a substrate bearing a bigger protective group attached to the primary hydroxyl group.

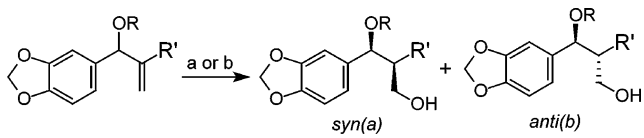
Unfortunately, attempts to separate these diastereomers, at this stage, failed. To prepare the acid **5**, the mixture of diastereomers was then treated with PDC in DMF.[22] Surprisingly, after 20 h we were able



Scheme 1. Retrosynthetic analysis for preparation of oxazolidin-2-ones.



Scheme 2. (a) TIPSOTf, CH_2Cl_2, 2,6-lutidine, rt, 30 min, 95%; (b) DIBAL-H, CH_2Cl_2, −78°C, 2 h, 91%; (c) TBSOTf, CH_2Cl_2, 2,6-lutidine, rt, 30 min, 100% or (d) TBDPSCl, imidazole, DMF, rt, 14 h, 90%.



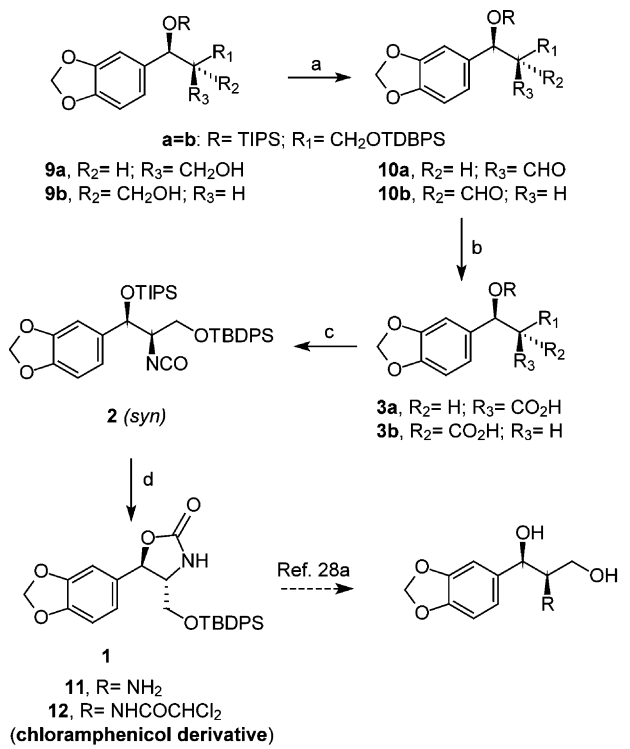
Substrate	$BH_3.S(CH_3)_2$	Yield (%)	9-BBN	Yield (%)
4	*syn:anti* (**8a/b**; 50:50)	85	*syn:anti* (**8a/b**; 60:40)	70
7	*syn: anti* (**9a/b**; 50:50)	60	*syn: anti* (**9a/b**; 80:20)	89

Scheme 3. (a) (i) $BH_3{\cdot}(CH_3)_2$, THF, 0°C→rt, 16 h; (ii) NaOH 3 M, H_2O_2 30%, 0°C→rt, 1.5 h; (b) (i) 9-BBN, THF, 0°C→rt, 16 h; (ii) NaOH 3 M, H_2O_2 30%, 0°C→rt, 1.5 h.

to isolate a mixture of aldehyde **10** with the required acid **3**, in very low concentration (>10%). To drive this reaction to completion, we increased the reaction time and PDC concentration. However, after 48 h only degradation products were detected. The same behaviour was observed when PDC was replaced by Jones reagent (diluted reagent at 0°C).[23]

Due to the difficulties in directly transforming the mixture of diastereoisomeric alcohols **9a**/**b** into acids **3a**/**b**, we decided to carry it out in two steps. Thus, **9a**/**b** was treated with tetrapropylammonium perruthenate (TPAP), in the presence of 4-methylmorpholine *N*-oxide (NMO),[24] to give the aldehydes **10a**/**b** in 96% yield. Subsequently these aldehydes were oxidised with sodium chlorite (Pinnick reaction)[25] to furnish the acids **3a**/**b**, in 90% yield. Fortunately, the carboxylic acids were easily separated by flash column chromatography (Scheme 4).

To determine the relative stereochemistry obtained in the hydroboration step, we removed the protective groups from the separated acids **3a** and **3b** with TBAF/THF. The resulting diol-acids were transformed into the corresponding dimethylacetals (2,2-dimethoxypropane, CSA) and the coupling constant for the carbinolic protons in both diastereomers was measured.[26] This NMR experiment allowed us to confirm that, for both cases where we have observed diastereoselectivity, the *syn* diastereomer was preferentially formed.



Scheme 4. (a) TPAP, NMO, CH_2Cl_2, MS 4 Å, 15 min, rt, 96%; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methyl-but-2-ene, rt, 14 h, 90%, chromatographic separation; (c) (i) $ClCO_2Et$, NEt_3, 0°C, 40 min; (ii) NaN_3, H_2O, 0°C, 2 h; (iii) reflux in toluene; (d) $SnCl_4$, CH_2Cl_2, rt, 16 h, 30% overall yield (five steps).

We tried to prepare the isocyanate **2** by the direct treatment of acid **3a** with diphenylphosphorylazide (DPPA)[27] in refluxing toluene/methanol in the presence of triethylamine; however, all attempts were unsuccessful. Thus, acid **3a** was successively treated with ethyl chloroformate and sodium azide to provide an intermediate acylazide, which was not isolated. Reflux in toluene gave the isocyanate **2** (not isolated) (Scheme 4).

Isocyanate **2** was then treated with tin tetrachloride in dichloromethane to furnish oxazolidin-2-one (**1**) as the only detectable product, in 30% overall yield (five steps). This simple and straightforward sequence permitted us to synthesise the required oxazolidin-2-one in eight steps, with an overall yield of 26%, from Baylis–Hillman adduct (**5**).[28]

To shorten the synthetic sequence we tried to effect the Curtius rearrangement directly on the Baylis–Hillman adduct **5**. Unfortunately, under the experimental conditions used, the rearrangement did not work.

As far as we know, this is the first report concerning the utilisation of a Baylis–Hillman adduct as starting material for the preparation of oxazolidin-2-ones. This strategy has culminated with the preparation of our target compound **1**, whose biological profile is under investigation.

Since we had **1** available, we decided to expand the scope of our synthetic sequence. Chloramphenicol and derivatives[29] are antibacterial agents used against different infections. Despite the elevated toxicity of this class of antibiotics, they are still in wide use topically (occular bacterial infections) and to combat certain types of infections (e.g. typhus, dysenthery). Recently, Park et al.[29a] have used a similar oxazolidinone as a key intermediate for the synthesis of chloramphenicol.

From our point of view, the preparation of **12** (Scheme 4) could be formally considered as achieved, since the preparation of aminoalcohols from an oxazolidinone and amidation of the latter are well documented synthetic methods.

In conclusion, we have developed a new approach for the preparation of functionalised oxazolidin-2-ones from the Baylis–Hillman adduct. Despite the moderate diastereoselectivity attained, this method seems to exhibit a high synthetic potential. In principle, depending on the structure of the aldehyde used in the Baylis–Hillman reaction, it is possible to prepare a wide range of 4,5-disubstituted oxazolidin-2-ones. In addition, if we simply invert the protective groups it is possible to exclusively gain access to 4-substituted oxazolidin-2-ones.

Additional studies are ongoing in our laboratory with the objective of generalising and optimising this strategy, to have a new general method to prepare substituted oxazolidin-2-ones and vicinal aminoalcohols, with potential biological activity, from Baylis–Hillman adduct.

Acknowledgements

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References

1. Danielmeier, K.; Steckhan, E. *Tetrahedron: Asymmetry* **1995**, *6*, 1181–1190.
2. (a) Prücher, H.; Gottschlich, R.; Haase, A.; Stohrer, M.; Seyfried, C. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 165–170; (b) Maj, J.; Rogoz, Z.; Skuza, G.; Mazela, H. *Eur. J. Pharmacol*. **1996**, *315*, 235–243.
3. Jarreau, F. X.; Koenig, J. J.; Rovei, V. *Eur. Pat. Appl*. EP 511,031,18. Oct. 1992 (*CAS* **1993**, *118*, 147549z).
4. Walsh, D. A.; Yanni, J. M. *US Patent* 5,086,055, 04.Feb. 1992 (*CAS* **1992**, *116*, 188072r).
5. (a) Gregory, W. A.; Britelli, D. R.; Wang, C. L. J.; Wuonola, M. A.; McRipley, R. J.; Eustine, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem*. **1989**, *32*, 1673–1681; (b) Eustice, D. C.; Brittelli, D. R.; Feldman, P. A.; Brown, L. J.; Borkowshi, J. J.; Slee, A. M. *Drugs Exp. Chim. Res*. **1990**, *16*, 149–155; (c) Brickner, S. J. *Curr. Pharm. Design* **1996**, *2*, 175–194.
6. Albright, J. D.; Sun, F. W. *Eur. Pat. Appl*. WD 93 20,073, 14.Oct. 1993 (*CAS* **1994**, *120*, 106761k).
7. Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc*. **1993**, *115*, 11446–11459.
8. Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc*. **1990**, *112*, 2998–3017.
9. For some examples of the use of oxazolidin-2-ones as chiral auxiliary, see: (a) Gaul, C.; Scharer, K.; Seebach, D. *J. Org. Chem*. **2001**, *66*, 3059–3073; (b) Yamamoto, H.; Watanabe, S.; Kadotani, K.; Hasegawa, M.; Noguchi, M.; Kanemasa, S. *Tetrahedron Lett*. **2000**, *41*, 3131–3136; (c) Faita, G.; Paio, A.; Quatrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett*. **2000**, *41*, 1265–1269. (d) Rosenstein, I. J.; Tynan, T. A. *Tetrahedron Lett*. **1998**, *39*, 8429–8432; (e) Gibson, C. L.; Gillon, K.; Cook, S. *Tetrahedron Lett*. **1998**, *39*, 6733–6756; (f) Nakamura, T.; Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett*. **1997**, *38*, 559–562; (g) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3–12; (h) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835–875; (i) Ishizuka, T.; Kunieda, T. *J. Syn. Org. Chem. Jpn*. **1995**, *53*, 95–103.
10. (a) Diekema, D. J.; Jones, R. N. *Lancet* **2001**, *358*, 1975–1982; (b) Shinabarger, D. L.; Marotti, K. R.; Murray, R. W.; Lin, A. H.; Melchior, E. P.; Swaney, S. M.; Dunyak, D. S.; Demyan, W. F.; Buysse, J. M. *Antimicrob. Agents Chemother*. **1997**, *41*, 2132–2136; (c) Tokuyama, R.; Takahashi, Y.; Tomita, Y.; Suzuki, T.; Iwasaki, N.; Kado, N.; Okezaki, E.; Nagata, O. *Chem. Pharm. Bull*. **2001**, *49*, 347–352; (d) Marchese, A.; Schito, G. C. *Clin. Microbiol. Infect*. **2001**, *7* (suppl 4), 66–74.
11. ten Holte, P.; van Esseveldt, B. C. J.; Thijs, L.; Zwanenburg, B. *Eur. J. Org. Chem*. **2001**, 2965–2969.
12. Borman, S. *Chem. Eng. News* **2000**, *29* (May), 12–12.
13. (a) Dyen, M. E.; Swern, D. *Chem. Rev*. **1967**, *67*, 197–246; (b) Ozaki, S. *Chem. Rev*. **1972**, *72*, 457–496.
14. Sibi, M. P.; Rutherford, D.; Sharma, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1675–1678.
15. Qian, C.; Zhu, D. *Synlett* **1994**, 129–130.
16. Saito, N.; Hatakeda, K.; Ito, S.; Asano, T.; Toda, T. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 1629–1631.
17. Soga, K.; Hosoda, S.; Nakamura, H.; Ikeda, S. *J. Chem. Soc., Chem. Commun*. **1976**, *16*, 617–617.
18. Buchstaller, H. P. *Tetrahedron* **1998**, *54*, 3465–3470.
19. (a) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972 (C.*A*. **1972**, *77*, 34174q); (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (c) Ciganek, E. *Org. React*. **1997**, *51*, 201–350; (d) Almeida, W. P.; Coelho, F. *Quim. Nova* **2000**, *23*, 98–103 (*CA* **2000**, *132*, 236562e).
20. Almeida, W. P.; Mateus, C. R.; Coelho, F. *Tetrahedron Lett*. **2000**, *41*, 2153–2156.
21. Almeida, W. P.; Coelho, F. *Tetrahedron Lett*. **1998**, *39*, 8609–8612.
22. Corey, E. J.; Schmidt, G. *Tetrahedron Lett*. **1979**, *20*, 399–400.
23. (a) Duney, A. B.; Forsyth, C. J. *Org. Lett*. **1999**, *1*, 451–453; (b) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *J. Org. Chem*. **1996**, *61*, 566–572.
24. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
25. (a) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096; (b) Dalcanale, E.; Montanari, F. *J. Org. Chem*. **1986**, *51*, 567–569; (c) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand*. **1973**, *27*, 888–890.
26. (a) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 3rd ed.; Wiley-VCH: New York, 1998, p. 90; (b) For the diastereoisomer *anti* we observed a constant of 11 Hz for the coupling of the benzylic proton with the proton in the α position of the carboxylic acid group (diaxial).
27. (a) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem*. **1997**, *62*, 5864–5872; (b) Burgess, K.; Lim, D.; Ho, K. K.; Ke, C. Y. *J. Org. Chem*. **1994**, *59*, 2179–2185; (c) Dekimpe, N.; Boeykens, M.; Tehrani, K. A. *J. Org. Chem*. **1994**, *59*, 8215–8219; (d) Thornton, T. J.; Jarman, M. *Synthesis* **1990**, 295–299; (e) Leenders, R. G. G.; Ruytenbeck, R.; Damen, E. W. P.; Scheeren, H. W. *Synthesis* **1996**, 1309–1312.
28. Spectral data: **1** IR ($\nu/_{max}$, film); 3224, 1758, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.67 (m, 10H), 6.65–6.85 (m, 3H), 5.98 (s, 2H), 5.44 (bs, NH), 5.18 (d, $J=5.0$ Hz, 1H), 3.70–3.80 (m, 3H), 1.07 (s, 9H); ^{13}H NMR (75.4 MHz, $CDCl_3$) δ 158.6, 148.4, 148.2, 135.6, 132.7, 132.5, 130.2, 128.1, 119.7, 108.4, 106.2, 101.4, 79.8, 64.9, 61.5, 26.7, 19.1; HRMS (M^+) Calcd for $C_{27}H_{29}NO_5Si$: 475.181501. Found: 475.18115; **3a** IR ($\nu/_{max}$, film); 3135, 3077, 1714, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.70 (m, 10H), 6.50–6.80 (m, 3H), 5.95 (m, 2H), 5.06 (d, $J=7.0$, 1H), 3.70 (dd, $J=10$ and 8 Hz), 3.56 (dd, $J=10$ and 5 Hz, 1H), 2.95 (ddd, $J=8$, 5 and 7 Hz), 0.80–1.20 (m, 30H).
29. For some recent examples of chloramphenicol syntheses, see: (a) Park, J. M.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett*. **2000**, *41*, 5553–5556; (b) Corey, E. J.; Choi, S. *Tetrahedron Lett*. **2000**, *41*, 2765–2768; (c) Veeresa, G.; Datta, A. *Tetrahedron Lett*. **1998**, *39*, 8503–8504 and references cited therein.