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Tetrahedron Letters
Tetrahedron Letters 45 (2004) xxx–xxx

Stereoselective synthesis of the C_9–C_{19} lactone-dipropionate fragment of calyculin C

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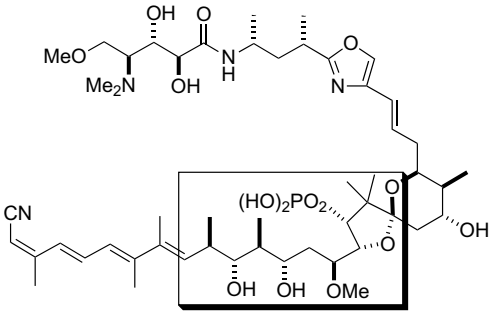
Received 23 June 2004; revised 24 August 2004; accepted 2 September 2004

Abstract—A highly diastereoselective synthesis of the title fragment of calyculin C has been developed based on an internal asymmetric induction between a chiral aldehyde and *Z*-crotyl trifluorosilane.

Calyculins form a class of highly cytotoxic metabolites from the marine sponge *Discodermia calyx* originally isolated by Fusetani and co-workers.[1] They have proven to be strong serine/threonine protein phosphatase inhibitors[2] and based on this property, calyculins might be potential anti-cancer agents.[3]

The C_9–C_{19} lactone-dipropionate fragment **5** of calyculin C (boxed in Fig. 1) contains 8 out of the total of 16 stereocenters and is thereby a key substructure of this sponge metabolite.



Calyculin C

Figure 1.

Several different syntheses of this fragment have been published with varying strategies.[4] The most challenging part in the synthesis of this C_9–C_{20} fragment is the *anti*,*anti*,*anti*-stereotetrad, which can be reached either by linear[4e,d] or by convergent[4a–c] approaches. However, the syntheses published so far have many weaknesses (too many steps, poor diastereoselectivity, or need for inversion of stereocenters). Therefore, improved routes to this fragment are still needed.

We have recently published a convergent approach toward the C_9–C_{19} fragment[5] of calyculin C, which unfortunately led to a wrong diastereomer. In this communication we would like to present a short, highly diastereo-, and enantioselective linear synthesis of the lactone-dipropionate fragment **5** of calyculin C.

Our synthesis of C_9–C_{19} fragment of calyculin C is based on a short and highly enantioselective synthesis of the key intermediate **1**[5] followed by two asymmetric crotylation reactions (Scheme 1). Armstrong and co-workers have used a similar strategy in their synthesis of the C_9–C_{25} fragment of calyculin[6] but in the last crotylation step they obtained only a disappointing 1:1.3 diastereoselection. We wished to improve this selectivity by using *Z*-crotyl trifluorosilane as the crotylation reagent in the second crotylation step.[7]

The synthesis of the key intermediate **1** is shown in Scheme 2.[5] The first crotylation reaction was realized with the crotyl borane derived from *E*-butene and (+)-MeOB(Ipc)$_2$ (Scheme 3).[8] The reaction yielded a 6:1 mixture of two diastereomeric *anti*-homoallylic alcohols, the major product[8] being isolated from the mixture by

Keywords: Aldol reactions; Crotylation; Diastereoselectivity; Natural products; Stereoselective synthesis.
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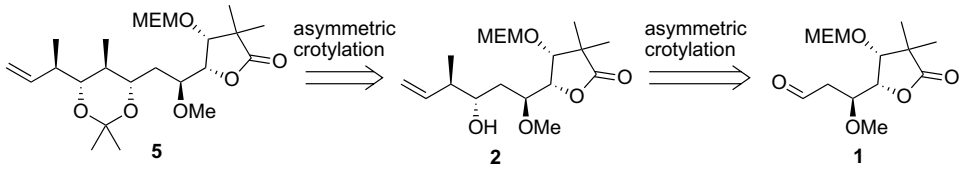
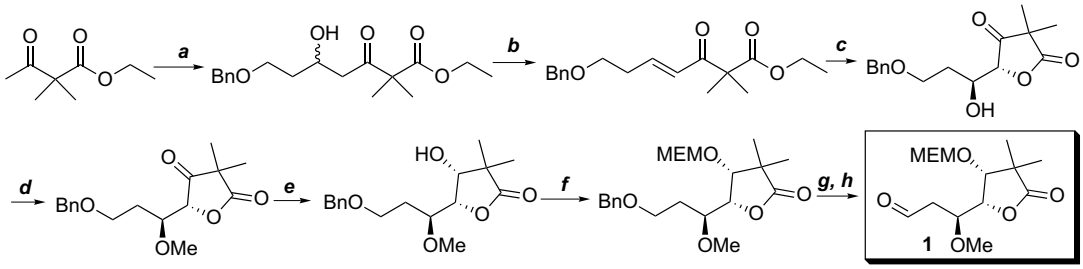
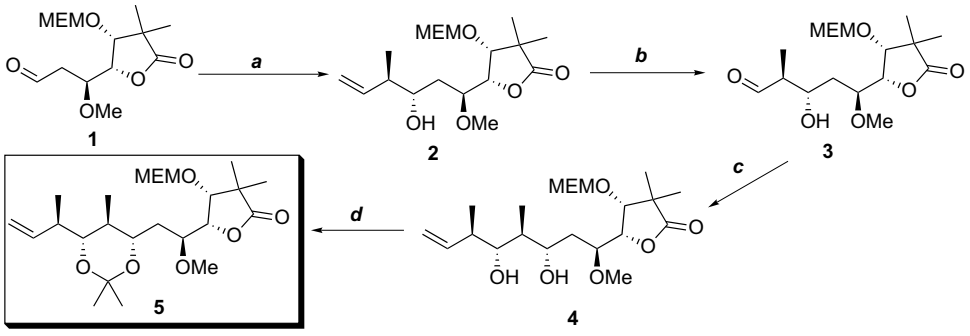
doi:10.1016/j.tetlet.2004.09.012



Scheme 1.



Scheme 2. Reagents and conditions: (a) i. LDA, THF, −78 °C, 1 h, ii. $PhCH_2OCH_2CH_2CHO$, −78 °C, 1 h, 75%; (b) NEt_3, MsCl, CH_2Cl_2, 0 °C, 3.5 h, 85%; (c) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 17 h, 78% quantitative, 91% ee after crystallization; (d) Ag_2O, MeI, Et_2O, reflux, 21 h, 62%; (e) L-Selectride, THF, −78 °C, 10 min, 58–69%; (f) DIPEA, MEMCl, CH_2Cl_2, reflux, 44 h, 73–87%; (g) $Pd(OH)_2/C$, H_2, EtOH, rt, 0.5 h, 91% quantitative; (h) TPAP, NMO, CH_2Cl_2, rt, 0.5 h, 65–75%.

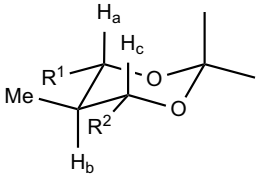


Scheme 3. Reagents and conditions: (a) i. the crotyl reagent was prepared from (+)-IpcBOMe and *E*-butene in THF at −78 °C, ii. $BF_3{\cdot}OEt$, the aldehyde **1**, −78 °C, 1 h, iii. ethanolamine; (b) i. O_3, CH_2Cl_2, −78 °C, ii. triphenylphosphine, rt, 3 h; (c) i. aldehyde **3**, 4 Å MS, CH_2Cl_2, rt, 0.5 h, ii. 0 °C, DIPEA, *Z*-crotyl trifluorosilane, 4 h; (d) 2-methoxypropene, pyridinium *p*-toluenesulfonate (PPTS) (cat.), CH_2Cl_2, rt, 0.5 h.

simple flash chromatography. The homoallylic alcohol **2** was then treated with O_3 to furnish the corresponding β-hydroxy aldehyde **3**[9] (Scheme 3). The final crotylation was performed with *Z*-crotyl trifluorosilane.[10,11] The existing hydroxyl group directs the stereochemistry toward the *anti*,*anti*,*anti*-stereotetrad without any external source of chirality.[7] This crotylation produced a single diastereomer **4**[12] based on the ^1H NMR spectrum of the crude product. Finally the diol **4** was converted to the corresponding ketal **5**.[13]

The ^1H and ^{13}C NMR analyses revealed the relative stereochemistry of the ketal ring (Fig. 2). The ^{13}C spectrum provided strong evidence for a *syn*-1,3-diol relationship[14] while the couplings in the ^1H NMR spectrum and NOESY correlations revealed the axial–axial relationship of the protons in the ketal ring.

The spectroscopic evidence together with the known facts about the two crotylation reactions[6,7] lead us to propose that the stereochemistry of the stereotetrads in **4** and **5** has to be *anti*,*anti*,*anti*.



^1H: *J* (Ha-Hb) = 11.1, *J* (Hb-Hc) = 9.8
^{13}C chemical shifts:
acetonide acetal 97.1 ppm
acetonide methyls 30.1 and 19.6 ppm

Figure 2.

These preliminary results of the synthesis of the challenging *anti*,*anti*,*anti*-dipropionate structure of calyculin C are very important in the field of natural product total synthesis. The *anti*,*anti*,*anti*-stereochemistry was achieved in only three steps with satisfactory diastereoselectivity. The crotylation methodology (*Z*-crotyl trifluorosilane) recently developed by Chemler and Roush[7]

proved to be a useful reaction in the synthesis of the *anti*,*anti*,*anti*-stereotetrad. Scaling up and optimization of the reactions are currently under way.

Acknowledgements

Financial support from the Finnish Academy is gratefully acknowledged.

References and notes

1. Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 2780.
2. Sheppeck, J. E., II; Gauss, C.-M.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739.
3. Bridges, A. J. *Chemtracts-Org. Chem.* **1995**, *8*, 73.
4. (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434; (b) Yokokawa, F.; Hamada, Y.; Shiori, T. *Chem. Commun.* **1996**, 871; (c) Smith, A. B.; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qui, Y.; Spoors, P. G.; Bertonesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596; (d) Ogawa, A. K.; Armstrong, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 12435; (e) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed.* **1994**, *33*, 673.
5. Karisalmi, K.; Koskinen, A. M. P. *Synthesis* **2004**, 1331.
6. Scarlato, G.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139.
7. Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319.
8. Compound **2**: *t*-BuOK (42 mg, 0.37 mmol, 150 mol%) was suspended in dry THF (1.5 mL) in a flame-dried flask under Ar and this mixture was cooled to −78 °C. Excess *E*-butene (condensed in another flask) was added via cannula, followed by *n*-BuLi (0.185 mL, $c = 2.0$ M, 0.37 mmol, 150 mol%). The yellow mixture was stirred at −45 °C for 15 min, then re-cooled to −78 °C and $(Ipc)_2$-BOMe (158 mg, 0.5 mmol, 200 mol%) in 1 mL of THF was added via cannula (the yellow color disappeared). This mixture was stirred at −78 °C for 1/2 h, then $BF_3{\cdot}OEt$ (41 mL, 0.325 mmol, 130 mol%) and aldehyde **1** (75 mg, 0.25 mmol, 100 mol%) were added. After 1 h the reaction mixture was concentrated and re-dissolved in 3 mL of dry Et_2O, cooled in an ice-bath and 15 mL of ethanolamine was added. The mixture was stirred at rt over night, filtered through Celite, and purified by flash chromatography (60% EtOAc–hexane). 19 mg (21%) of a 6:1 mixture of two diastereomers was isolated and the major diastereomer (12 mg) was obtained in pure form after second mini-flash purification (15% IPA–hexane). R_f 0.2 (60% EtOAc–hexane, PMA stain); $[\alpha]_D$ +4.2 (c 1.0, $CHCl_3$); IR (film) 3502, 1776 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.04 (3H, d, $CH_2{=}CHCHC\mathit{H}_3R$, $J = 6.9$), 1.24 (6H, s, $RCOCC\mathit{H}_3C\mathit{H}_3COO$), 1.56 (1H, ddd, $OHCHC\mathit{H}_aH_b$-CHOMe, $J = 14.7$, 9.8, 6.9), 1.81 (1H, ddd, $OHCH$-$CH_a\mathit{H}_bCHOMe$, $J = 14.7$, 4.5, 1.8), 2.17–2.26 (1H, m, $CH_2{=}CHC\mathit{H}CH_3R$), 3.38 (3H, s, $C\mathit{H}_3OCH_2CH_2R$), 3.51–3.58 (2H, m, $CH_3OC\mathit{H}_2R$), 3.51 (3H, s, $C\mathit{H}_3OR$), 3.65–3.81 (4H, m, $CHOHCH_2CHOMe + CH_3OCH_2CH_2R$), 4.02 (1H, d, $RC\mathit{H}OMEM$, $J = 4.2$), 4.49 (1H, dd, $R_2C\mathit{H}OCOR$, $J = 4.2$, 7.8), 4.68 (1H, d, $OC\mathit{H}_aH_bO$, $J = 6.7$), 4.78 (1H, d, $OCH_a\mathit{H}_bO$, $J = 6.7$), 5.06–5.12 (2H, m, $C\mathit{H}_2{=}CH$), 5.75–5.84 (1H, ddd, $CH_2{=}C\mathit{H}R$, $J = 16.8$, 11.0, 8.1); δ_C (100 MHz, $CDCl_3$): 16.0, 18.9, 23.3, 33.2, 44.5, 45.1, 59.0, 68.4, 71.6, 72.4, 79.0, 82.5, 83.4, 97.2, 115.9, 140.1, 180.1; HRMS *m/z* calcd for $C_{18}H_{32}O_7$ + Na: 383.2046; found: 383.2051($M+Na^+$).
9. Compound **3**: olefin **2** (15 mg, 0.042 mmol, 100 mol%) was dissolved in CH_2Cl_2 (3 mL) in a flame-dried flask, the mixture was cooled to −78 °C, and ozone was bubbled through the mixture until a blue color persisted (2 min). Then O_2 was bubbled through the mixture until the color disappeared, after which triphenylphosphine (16 mg, 0.062 mmol, 150 mol%) was added, the cooling bath was removed and the mixture was stirred at rt for 3 h. The solvent was evaporated in vacuo and the crude product was purified by mini-flash (15% to >30% IPA–hexane) and 9 mg (60%) of the β-hydroxyaldehyde was obtained. R_f 0.06 (15% IPA–hexane, PMA stain); $[\alpha]_D$ −3.1 (c 0.75, $CHCl_3$); IR (film) 3436, 1772, 1722 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.16 (3H, d, $O{=}CHCHC\mathit{H}_3R$, $J = 7.2$), 1.26 (6H, s, $RCOCC\mathit{H}_3C\mathit{H}_3COO$), 1.69 (1H, dd, $OHCHC\mathit{H}_aH_bCHOMe$, $J = 14.6$, 7.8), 1.93 (1H, ddd, $OHCHCH_a\mathit{H}_bCHOMe$, $J = 14.6$, 4.1, 2.0), 2.47–2.52 (1H, m, $O{=}CHC\mathit{H}CH_3R$), 3.38 (3H, s, $C\mathit{H}_3OCH_2CH_2R$), 3.51–3.58 (2H, m, $CH_3OC\mathit{H}_2R$), 3.55 (3H, s, $C\mathit{H}_3OR$), 3.60–3.67 (2H, m, $CH_3OCH_2C\mathit{H}_aH_bR$, $O\mathit{H}$), 3.72–3.76 (1H, m, $CH_3OCH_2CH_a\mathit{H}_bR$), 3.85 (1H, td, $CH_2C\mathit{H}O$-MeR_2, $J = 7.8$, 4.1), 4.02 (1H, d, $RC\mathit{H}OMEM$, $J = 4.2$), 4.08–4.12 (1H, m, $O{=}CHCHCH_3CHOHR$), 4.54 (1H, dd, $R_2C\mathit{H}OCOR$, $J = 7.8$, 4.2), 4.68 (1H, d, $OC\mathit{H}_aH_bO$, $J = 6.5$), 4.78 (1H, d, $OCH_a\mathit{H}_bO$, $J = 6.5$), 9.77 (1H, d, $R\mathit{H}C{=}O$, $J = 2.0$); δ_C (100 MHz, $CDCl_3$): 10.5, 18.8, 23.3, 33.5, 45.1, 52.0, 59.0, 59.3, 68.3, 70.7, 71.7, 78.8, 82.6, 83.2, 97.2, 179.9, 205.0; HRMS *m/z* calcd for $C_{17}H_{30}O_8$ + Na: 385.1838; found: 385.1806 ($M+Na^+$).
10. Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099.
11. Personal communication with Professor Sherry Chemler.
12. Compound **4**: β-hydroxy aldehyde **3** (3 mg, 8.26 mmol, 100 mol%) was dissolved in CH_2Cl_2 (0.6 mL) in a pear-shaped flame-dried flask under Ar together with 10 mg of crushed and activated 4 Å molecular sieves. The mixture was stirred at rt for 25 min, then cooled in an ice-bath, after which DIPEA (4 mL, 0.025 mmol, 300 mol%) and *Z*-crotyl trifluorosilane (4 mL, 0.026 mmol, 320 mol%) were added. After 4 h stirring at 0 °C the reaction was complete and it was quenched with satd NH_4Cl. The mixture was extracted 3 * EtOAc, the combined organic phase were dried over Na_2SO_4, the drying agent was filtered, and the solvent evaporated in vacuo. After purification with mini-flash (15% IPA–hexane) 1–2 mg of the desired *anti*, *anti*,*anti* aldol product was obtained. R_f 0.55 (30% IPA–hexane, PMA stain); $[\alpha]_D$ +4.6 (c 0.13, $CHCl_3$); IR (film) 3468, 1773 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.85 (3H, d, $CHOHCHC\mathit{H}_3CHOH$, $J = 6.8$), 1.12 (3H, d, $CH_2{=}CHCHC\mathit{H}_3R$, $J = 7.0$), 1.25 (6H, s, $RCOCC\mathit{H}_3C\mathit{H}_3COO$), 1.55–1.63 (1H, m, $OHCHC\mathit{H}_aH_bCHOMe$), 1.63–1.73 (1H, m, $CHOHC\mathit{H}CH_3CHOH$), 1.93 (1H, d, $OHCHCH_a\mathit{H}_b$-CHOMe, $J = 12.2$), 2.43–2.47 (1H, m, $CH_2{=}CHC\mathit{H}CH_3R$), 3.38 (3H, s, $C\mathit{H}_3OCH_2CH_2R$), 3.38–3.40 (1H, m, $CHCH_3C\mathit{H}OHCHCH_3$), 3.53–3.57 (2H, m, $CH_3OC\mathit{H}_2R$), 3.55 (3H, s, $C\mathit{H}_3OR$), 3.66–3.77 (2H, m, $CH_3OC\mathit{H}_2CH_2R$), 3.83 (1H, td, $CH_2C\mathit{H}OMeR_2$, $J = 7.8$, 4.4), 3.96 (1H, t, $CHCH_3C\mathit{H}OHCH_2$, $J = 7.8$), 4.00 (1H, d, $RC\mathit{H}OMEM$, $J = 4.4$), 4.54 (1H, dd, $R_2C\mathit{H}OCOR$, $J = 7.8$, 4.4), 4.67 (1H, d, $OC\mathit{H}_aH_bO$, $J = 6.5$), 4.84 (1H, d, $OCH_a\mathit{H}_bO$, $J = 6.5$), 5.06–5.12 (2H, m, $C\mathit{H}_2{=}CHR$), 5.90 (1H, ddd, $CH_2{=}C\mathit{H}R$, $J = 17.4$, 10.4, 8.2); δ_C (100 MHz, $CDCl_3$): 12.8, 17.8, 18.9, 23.4, 29.7, 40.7, 41.8, 45.1, 59.1, 59.4, 68.5, 71.8, 77.2, 78.1, 79.4, 82.7, 83.5, 97.4, 115.8, 139.0, 180.0; HRMS *m/z* calcd for $C_{21}H_{38}O_8$ + Na: 441.2464; found: 441.2449 ($M+Na^+$).

13. Compound **5**: diol **4** (1.5 mg, 3.54 mmol, 100 mol%) was dissolved in 0.2 mL of CH_2Cl_2 and 2-methoxypropene (2 mL, 17.9 mmol, 500 mol%) followed by pyridinium *p*-toluenesulfonate (PPTS) (cat.) were added. After 0.5 h the reaction was quenched with satd $NaHCO_3$, the mixture was extracted 3 * EtOAc, the combined organic phase were dried over Na_2SO_4, the drying agent was filtered, and the solvent evaporated. The crude product was not purified before analysis. R_f 0.5 (30% IPA–hexane, PMA stain); IR (film) 1776 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 0.76 (3H, d, CHORCHCH_3CHOR, $J = 6.6$), 1.05 (3H, d, CH_2=CHCHCH_3R, $J = 6.9$), 1.26 (6H, s, RCOCCH_3CH_3COO), 1.30 (3H, s, OC(C$H_3$$CH_3$)O), 1.40 (3H, s, OC($CH_3CH_3$)O), 1.37–1.40 (1H, m, OCH-CHCH_3CHO), 1.63 (1H, ddd, ORCHC$H_a$$H_b$CHOMe, $J = 14.9, 9.5, 2.5$), 2.05 (1H, ddd, ORCHC$H_a$$H_b$CHOMe, $J = 14.9, 5.7, 1.5$), 2.39–2.45 (1H, m, CH_2=CHC$H$$CH_3$R), 3.38 (1H, dd, CH_2=CHCHCH_3CHOR, $J = 9.8, 2.1$), 3.39 (3H, s, C$H_3$$OCH_2CH_2$R), 3.41–3.44 (1H, m, CH_3O-C$H_a$$H_b$$CH_2$OR), 3.42 (3H, s, C$H_3$OR), 3.53–3.56 (2H, m, $CH_3$$OCH_a$$H_b$$CH_a$$H_b$OR), 3.68 (1H, ddd, CH_2CHOMeR$_2$, $J = 8.2, 5.7, 2.5$), 3.69–3.74 (1H, m, $CH_3$$OCH_2CH_a$$H_b$OR), 3.76 (1H, dd, CHC$H_3CHORCH_2$, $J = 11.1, 9.5$), 4.14 (1H, d, RCHOMEM, $J = 3.8$), 4.54 (1H, dd, R$_2$CHOCOR, $J = 8.2, 3.8$), 4.72 (1H, d, OC$H_a$$H_b$O, $J = 7.0$), 4.79 (1H, d, OC$H_a$$H_b$O, $J = 7.0$), 4.97–5.03 (2H, m, CH_2=CHR), 5.84 (1H, ddd, CH_2=CHR, $J = 17.2, 10.3, 9.2$); δ_C (100 MHz, $CDCl_3$): 11.8, 18.0, 18.9, 19.6, 23.1, 30.1, 31.4, 35.7, 39.6, 45.5, 57.8, 59.1, 68.4, 69.5, 71.6, 77.2, 77.7, 82.0, 83.8, 97.1, 97.4, 114.9, 139.7, 180.3; HRMS *m/z* calcd for $C_{24}H_{42}O_8$ + Na: 481.2777; found: 481.2782 ($M+Na^+$).

14. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.