Tetrahedron 66 (2010) 4002–4009

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of triazole analogues of the nanaomycin antibiotics using 'click chemistry'

Kris Rathwell [a,b], Jonathan Sperry [a,b], Margaret A. Brimble [a,b,*]

[a] Department of Chemistry, University of Auckland, 23 Symonds Street, Auckland, New Zealand
[b] Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 4 February 2010
Received in revised form 26 March 2010
Accepted 12 April 2010
Available online xxx

Keywords:
Pyranonaphthoquinone
'Click chemistry'
Triazole
Nanaomycin

ABSTRACT

A series of triazole analogues of the nanaomycin family of antibiotics have been prepared using a 'click' dipolar cycloaddition of a naphthalene azide to various alkynes, followed by oxidation to the desired pyranonaphthoquinones.

1. Introduction

For all the biomedical promise of genetic engineering and combinatorial chemistry, nature continues to remain the key source of current pharmaceuticals and future drug candidates. By modification of a biologically active natural product, often libraries of simplified, non-natural compounds can be synthesised in order to improve the desired pharmacological activity.[1,2]

The pyranonaphthoquinone family of antibiotics display a wide range biological activity with medicinal potential.[3] One subclass within this family, the nanaomycins **1**–**6** are of particular interest due to their relatively simple, unique structure and biological activity thus rendering them attractive lead compounds (Fig. 1).

As part of an on-going screening program for *anti*-mycoplasmal antibiotics, Omura et al. isolated nanaomycins A **1**[4–6] B **2**,[4,5] C **3**,[7] D **4**[8] and E **5**[9] from *Streptomyces rosa*. Nanaomycins **1**–**5** possess a broad range of biological properties, including varying levels of inhibition against mycoplasma, fungi and Gram-positive bacteria.[4–9] In addition, nanaomycin A **1** has been shown to inhibit the platelet aggregation agent, adenosine diphosphate (ADP).[10] Furthermore, fermentation of a *Nocardia* species produced YS-02931K-β **6**, the enantiomer of nanaomycin A **1**. Compound **6** exhibited strong antimicrobial activity against Gram-positive bacteria as well as dermaphytes and fungi.[11–13] Some simplified

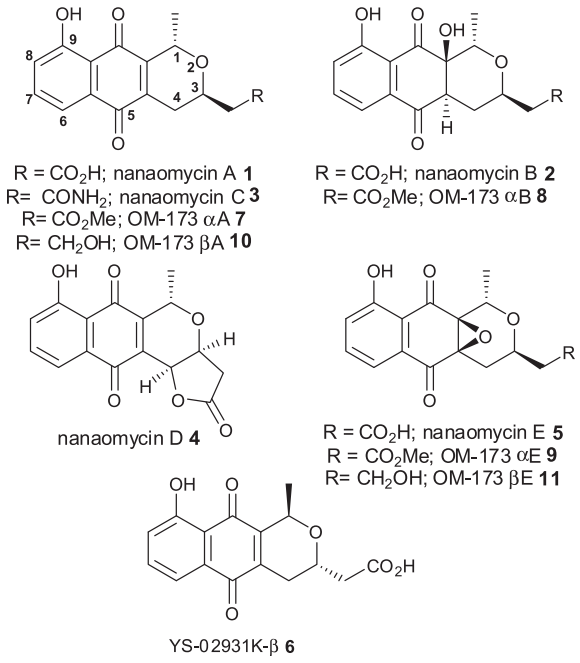
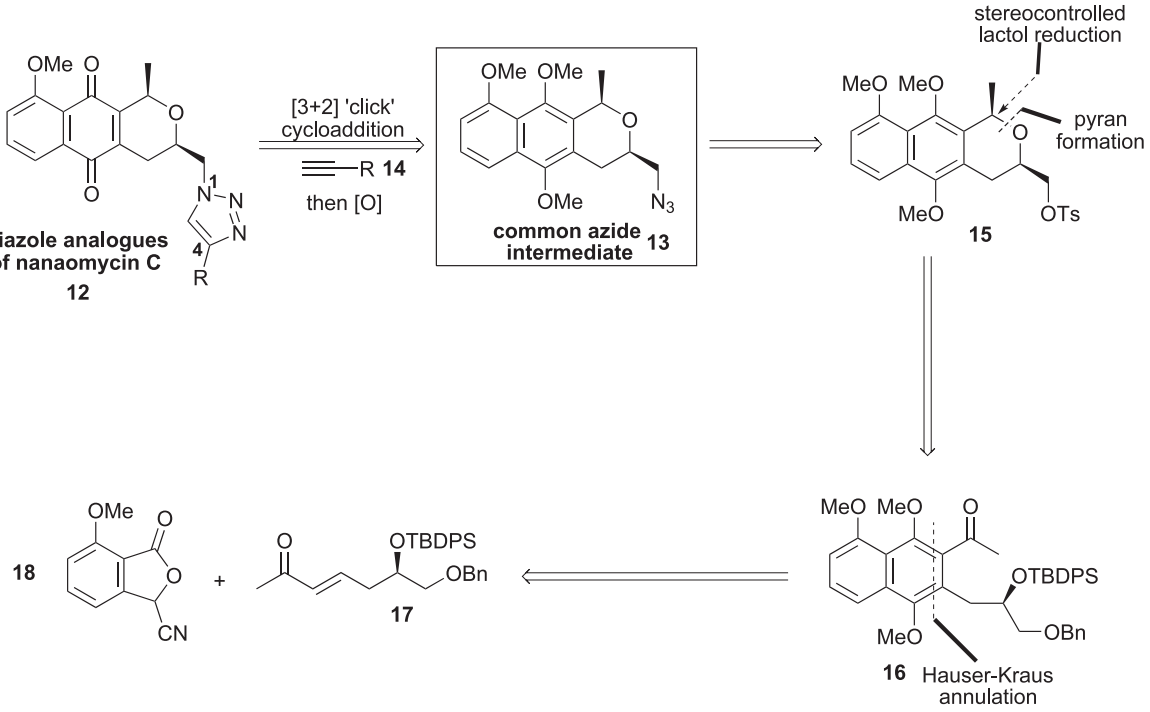


Figure 1. Nanaomycin family of pyranonaphthoquinone antibiotics.

* Corresponding author. E-mail address: m.brimble@auckland.ac.nz (M.A. Brimble).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.04.048



Scheme 1. Retrosynthesis of triazole analogues of the nanaomycins.

synthetic analogues of nanaomycins A **1** and D **4** were subsequently tested against various microorganisms for antibacterial properties, the results showing that the naphthoquinone and lactone moieties are the key pharmacophores.[14] Furthermore, the significantly reduced antimicrobial activity of the five nanaomycins isolated from a different strain of *S. rosa var. notoensis* (strain OM-173), namely OM-173 αA **7**, αB **8**, αE **9**, βA **10** and βE **11**, in which the carboxyl group is methylated or reduced to the corresponding hydroxymethyl moiety, established that the carboxyl group (or the cyclised γ-lactone) is indeed vital for the bioactivity to be maintained.[15]

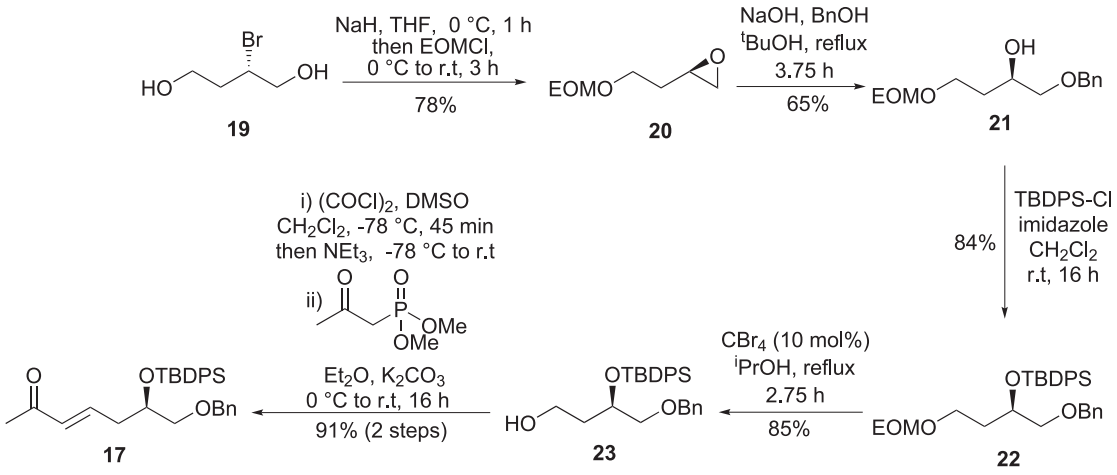
Guided by this bioactivity data, the synthesis of several 1,2,3-triazole mimics of the amide containing nanaomycin C **3** was initiated. Being a rigid linker, the triazole ring system holds the substituents in a similar geometry and distance to that of an amide, as well as providing a comparable dipole moment. However, unlike the amide counterpart, triazoles are stable towards hydrolytic cleavage (especially under enzymatic conditions), oxidation and reduction and thus display ideal characteristics to be successful therapeutic candidates in vivo.[16]

2. Results and discussion

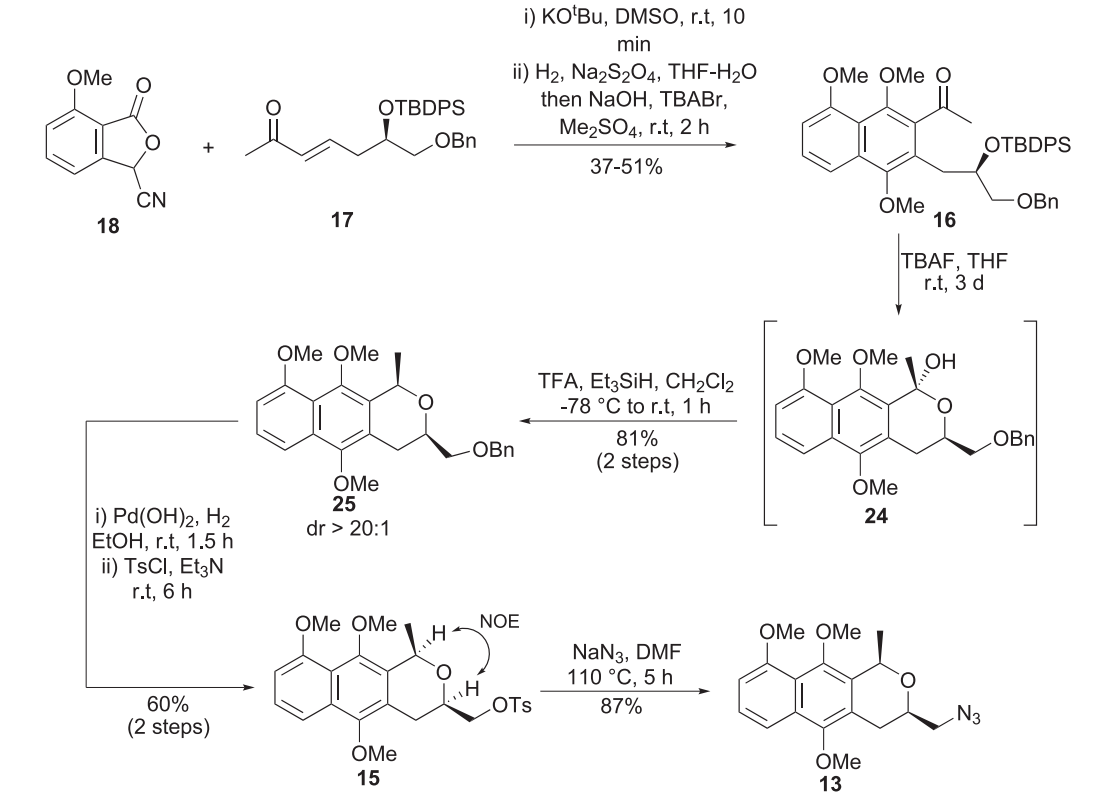
The retrosynthesis of various triazole analogues **12** is shown in Scheme 1 and centred on the enantioselective synthesis of *cis*-1,3-dimethylpyran-containing natural products developed in our laboratory.[17] Thus, azide **13** was envisaged to be a key intermediate upon which various dipolar cycloadditions could be conducted. Thus, the [3+2]-cycloaddition of azide **13** to various alkynes **14** in a 'click'-type process[18] delivers triazoles **12**. The azide itself is accessible by displacement of tosylate **15**, formed via intramolecular pyran formation and subsequent stereocontrolled lactol reduction.[19] A Hauser–Kraus annulation[20] between enone **17** and cyanophthalide **18** is initially used to construct naphthalene **16** (Scheme 1).

With cyanophthalide **18** already readily available in our laboratory,[17a] the synthesis of enone **17** was instigated. Bromodiol **19** was prepared from (*S*)-aspartic acid in two steps as described previously.[21] Base-mediated epoxide formation followed by treatment with EOMCl gave protected epoxide **20**. Successful opening of epoxide **20** with the alkoxide of benzyl alcohol delivered secondary alcohol **21**, which underwent smooth silylation furnishing **22**. Deprotection gave alcohol **23**, which underwent oxidation to the corresponding aldehyde followed by Horner–Wadsworth–Emmons olefination delivering the desired (−)-enone **17** in good overall yield (Scheme 2).

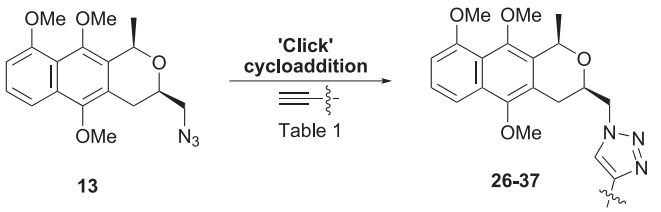
Next, the key annulation could be attempted. The Hauser–Kraus annulation between cyanophthalide **18** and (−)-enone **17** initially proved problematic, but it was found that isolating the crude annulation product after a very short reaction time (10 min) and immediately subjecting it to reductive methylation conditions furnished naphthalene **16** in modest overall yield. Treatment of **16** with excess TBAF for three days effected silyl group removal with concomitant cyclisation and the resulting crude lactol **24** was stereoselectively reduced with trifluoroacetic acid and triethylsilane delivering the *cis*-1,3-dimethylpyran **25** as a single diastereomer as determined by ^{1}H and ^{13}C NMR spectroscopy. Debenzylation under an atmosphere of hydrogen over Pearlman's catalyst followed by tosylation of the resulting crude alcohol gave tosylate **15**. At this stage, the 1,3-*cis* stereochemistry in **15** was confirmed by the NOE correlation between the axial protons at C1 and C3 on the pyran ring (see Supplementary data). Finally, displacement with sodium azide gave the key azide intermediate **13** (Scheme 3). With a scalable route to azide **13** in hand, attention turned to the key 'click' cycloadditions using a variety of alkynes (Scheme 4, Table 1). Gratifyingly, azide **13** underwent smooth cycloaddition with an excess of phenylacetylene and CuI[P(OEt)$_3$] (20 mol %)[22] in toluene upon heating to 85 °C, affording an excellent yield of the desired 1,4-disubstituted triazole **26** (entry 1). Several other substituted phenylacetylenes reacted smoothly under the same conditions (entries 2–5) affording **27**–**30**, as did benzylacetylene (entry 6) giving **31**. The cycloaddition of dimethyl acetylenedicarboxylate required forcing thermal conditions to proceed, delivering the 1,4,5-trisubstituted triazole **32** (entry 7). Reaction of azide **13**



Scheme 2. Synthesis of (−)-enone **17**.



Scheme 3. Synthesis of azide **13**.



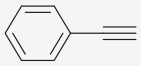
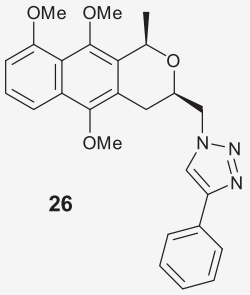
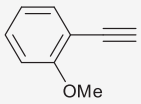
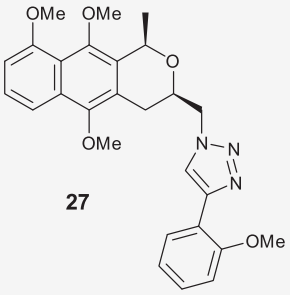
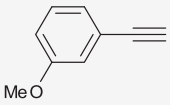
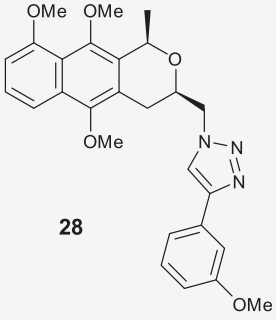
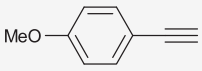
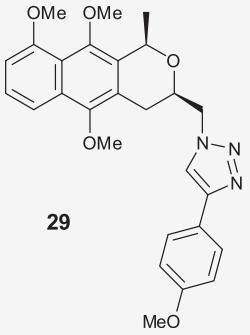
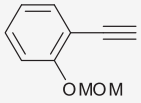
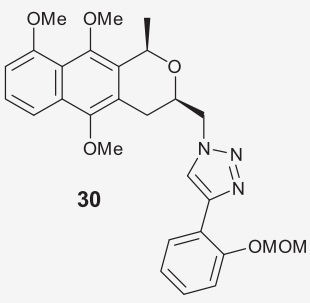
Scheme 4. Summary of 'click' cycloadditions between azide **13** and various alkynes.

with trimethylsilyl acetylene followed by cleavage with TBAF afforded the 1-substituted triazole **33** (entry 8). Azide **13** was also found to be compatible with the recently reported 'click' benzyne cycloaddition[23,24] (entry 9) giving **34**, representing one of the most synthetically complex azides to access benzotriazoles using this method to date. Cycloadditions using long chain alkynes (entries 10—**35** and 11—**36**) and a bis-alkyne (entry 12—**37**) were also successful.

As seen in Scheme 5 and Table 2, all of the triazole cycloadducts underwent smooth oxidation with either silver(II) oxide (Method A) or CAN (Method B) affording a series of nanaomycin triazole analogues **38**—**50**. The MOM-deprotection of **42** with $NaHSO_4$—SiO_2[25] also provided phenol-substituted analogue **43** (entry 6).

It was subsequently shown that the triazole analogue *cis*-**26** was compatible with the conditions required to effect epimerization to the more stable *trans*-isomer. Thus, triazole *cis*-**38** was treated with concentrated sulfuric acid in toluene at room temperature for 30 min, effecting epimerization and delivering *trans*-**38** possessing

Table 1
Summary of 'click' cycloadditions between azide **13** and various alkynes

Entry	Alkyne	Reagents and conditions[a]	Product	Yield (%)
1		**A** 1 h	 **26**	94
2		**A** 48 h	 **27**	74
3		**A** 5 h	 **28**	80
4		**A** 6.5 h	 **29**	88
5		**A** 48 h	 **30**	70

(*continued on next page*)

Table 1 (*continued*)

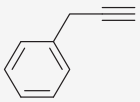
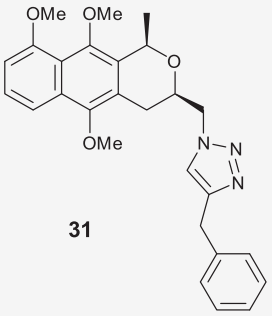
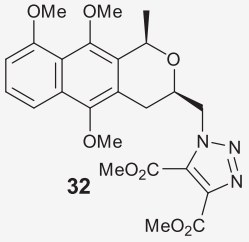
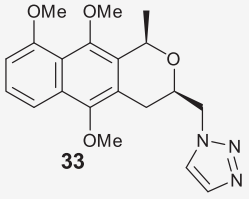
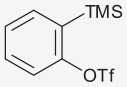
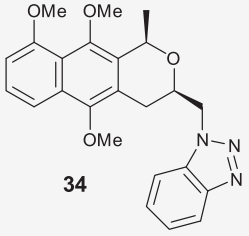
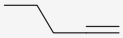
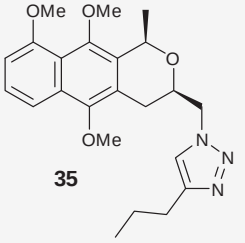
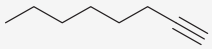
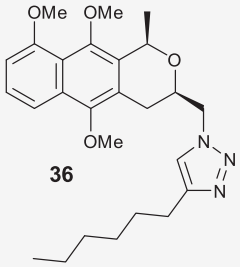
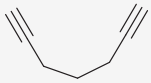
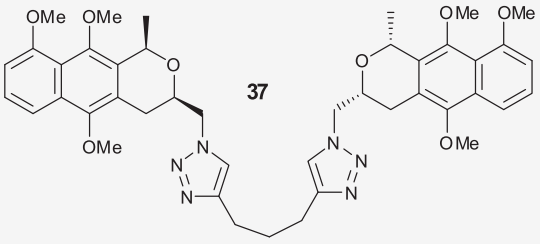
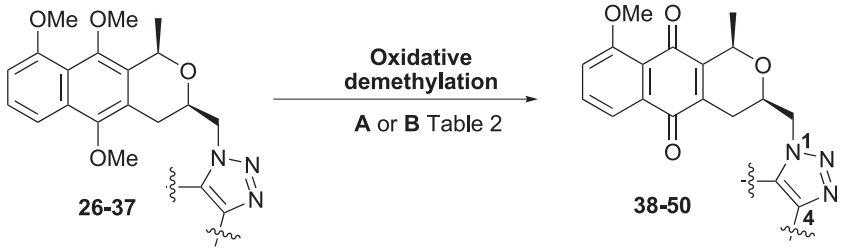
Entry	Alkyne	Reagents and conditions[a]	Product	Yield (%)
6		**A** 4.5 h	 **31**	71
7	MeO_2C—≡—CO_2Me	100 °C Neat 1.25 h	 **32**	86
8	—≡—TMS	**A**, 48 h then TBAF–AcOH THF	 **33**	60 (two steps)
9		CsF, 18-Crown-6, MeCN, 1 h 	 **34**	74
10		**A** 1.5 h	 **35**	93

Table 1 (*continued*)

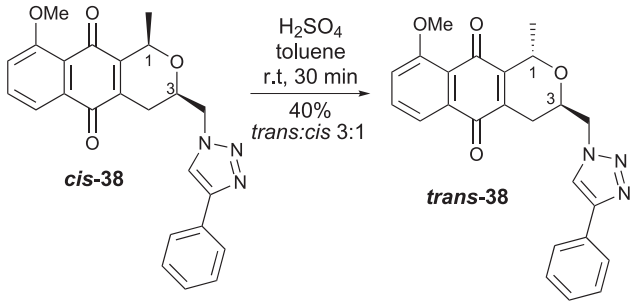
Entry	Alkyne	Reagents and conditions[a]	Product	Yield (%)
11		**A** 2.25 h	 **36**	81
12		**A** (0.5 equiv bis-alkyne) 23 h	 **37**	87

[a] Conditions **A**—Azide **13**, CuI[P(OEt)$_3$] (10–20 mol %), alkyne (1.2–5 equiv), toluene, 85 °C (See Supplementary data for full details).



Scheme 5. Oxidation to 'click' analogues of the nanaomycins.

the natural, C1–C3-*trans* stereochemistry present in the nanaomycins (Scheme 6).



Scheme 6. Epimerization of a triazole pyranonaphthoquinone.

3. Conclusions

In conclusion, we have prepared a series of triazole analogues of the nanaomycin family of antibiotics via a 'click' dipolar cycloaddition of a *cis*-1,3-disubstituted pyranonaphthalene azide to various alkynes, followed by oxidation to the desired pyranonaphthoquinones. Epimerization of *cis*-**38**, delivered triazole nanaomycin analogue *trans*-**38** possessing the natural 1,3-*trans*-pyran stereochemistry. Biological evaluation of these analogues is currently in progress.

4. Experimental

4.1. General

Full experimental details are provided in the Supplementary data. Details of a representative 'click' cycloaddition and oxidation steps are described herein.

4.1.1. 4-Phenyl-1-(((1R,3R)-5,9,10-trimethoxy-1-methyl-3,4-dihydro-1H-benzo[g]isochromen-3-yl)methyl)-1H-1,2,3-triazole (***26***). To a solution of azide **13** (27.3 mg, 0.08 mmol) in toluene (0.8 mL) was added phenylacetylene (25.1 mg, 0.24 mmol) and CuI[P(OEt)$_3$] (4.9 mg, 0.014 mmol). The reaction was stirred in a sealed vial at 85 °C for 1 h, concentrated in vacuo and purified by flash chromatography eluting with hexanes/ethyl acetate (2:1) to afford the *title compound* as a colourless solid (33.3 mg, 0.075 mmol, 94%); mp 68–72 °C; TLC (hexanes/ethyl acetate 2:1) R_f=0.17; $[\alpha]_D^{20}$ +130.2 (*c* 0.05, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2931, 2837, 1733, 1594, 1570, 1499, 1462, 1444, 1371, 1339, 1263, 1223, 1179, 1136, 1109, 1061, 1008; δ_H (400 MHz, $CDCl_3$) 1.66 (3H, d, *J* 6.3, CHC*H*$_3$), 2.59 (1H, dd, *J* 15.8 and 11.5, C*H*$_{ax}$H), 3.17 (1H, dd, *J* 15.8 and 1.6, CH*H*$_{eq}$), 3.74 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.99 (4H, s, OC*H*$_3$+*H*-3), 4.58 (1H, dd, *J* 14.2 and 7.0, C*H*HN), 4.78 (1H, dd, *J* 14.2 and 2.9, CH*H*N), 5.24 (1H, q, *J* 6.3, C*H*CH$_3$), 6.84 (1H, d, *J* 7.7, Ph*H*), 7.34–7.46 (4H, m, Ph*H*), 7.66 (1H, d, *J* 8.5, Ph*H*), 7.87–7.89 (2H, m, Ph*H*), 8.07 (1H, s, triazole); δ_C (100 MHz, $CDCl_3$) 23.2 (CH_3), 27.0 (CH_2), 54.6 (CH_2), 56.1 (CH_3), 61.3 (CH_3), 61.7 (CH_3), 71.5 (CH), 72.0 (CH), 105.7 (CH), 114.5 (CH), 119.5

Table 2
Oxidation to 'click' analogues of the nanaomycins

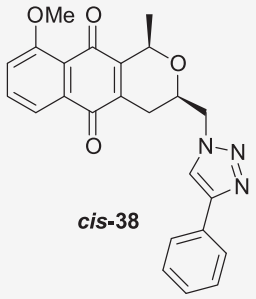
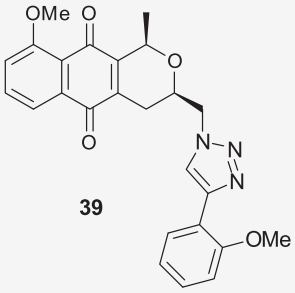
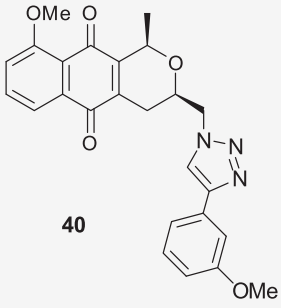
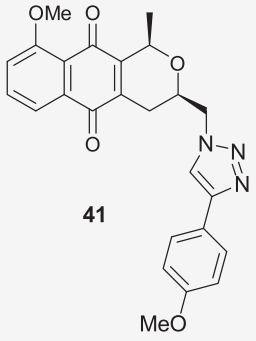
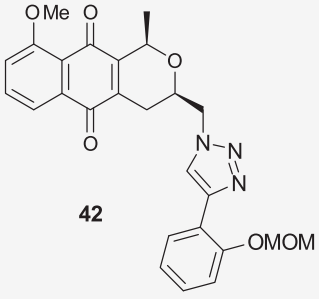
Entry	Starting material/ Method[a]	Product	Yield (%)
1	**26** **B**	 ***cis*-38**	72
2	**27** **A**	 **39**	83
3	**28** **A**	 **40**	82
4	**29** **A**	 **41**	90
5	**30** **A**	 **42**	90

Table 2 (*continued*)

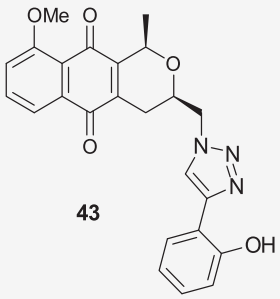
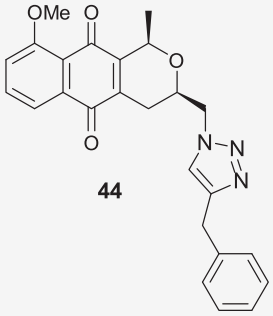
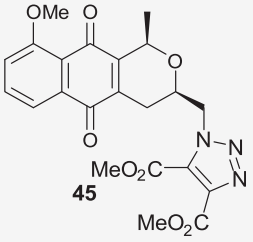
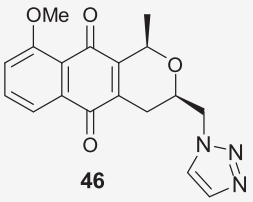
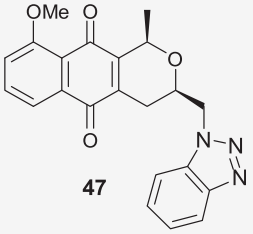
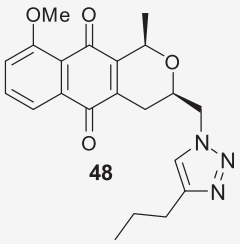
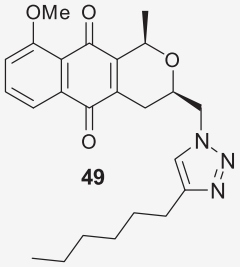
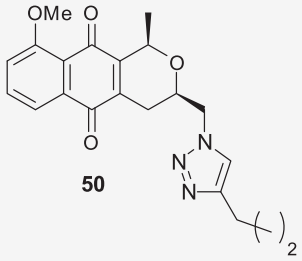
Entry	Starting material/ Method[a]	Product	Yield (%)
6	**42** $NaHSO_4$—SiO_2	 **43**	66
7	**31** **A**	 **44**	75
8	**32** **B**	 **45**	50
9	**33** **A**	 **46**	71
10	**34** **A**	 **47**	82

Table 2 (*continued*)

Entry	Starting material/ Method[a]	Product	Yield (%)
11	**35** **B**	 **48**	73
12	**36** **B**	 **49**	69
13	**37** **B**	 **50**	35

[a] Method **A**-AgO, HNO_3, dioxane, rt, Method **B**-CAN, $MeCN/H_2O$, rt, (See Supplementary data for full details).

(C), 121.2 (C), 123.9 (C), 125.7 (2×CH), 126.1 (CH), 128.1 (CH), 128.8 (2×CH), 129.1 (C), 129.9 (C), 130.8 (C), 147.7 (C), 148.9 (C), 149.1 (C), 156.0 (C); *m*/*z* (EI^+): 445 (100%, M^+), 414 (1), 402 (2), 386 (2), 370 (4), 342 (3), 300 (5), 285 (15), 271 (7), 243 (8), 229 (11), 213 (7), 159 (9), 130 (10), 116 (10), 102 (13), 89 (5), 77 (8), 57 (12), 43 (13); HRMS (EI^+, M^+) found 445.2003, calcd for $C_{26}H_{27}N_3O_4$ 445.2002.

*4.1.2. (1R,3R)-9-Methoxy-1-methyl-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-3,4-dihydro-1H-benzo[g]isochromene-5,10-dione (cis-**38**).* To a solution of the triazole **26** in acetonitrile (1.5 mL) was added a solution of cerium(IV) ammonium nitrate (70.6 mg, 0.13 mmol) in water (0.8 mL). The reaction was stirred for 50 min at room temperature, then partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, dried over magnesium sulfate and the solvent removed in vacuo. The crude oil was purified by column chromatography to afford the *title compound* as a yellow solid (18.6 mg, 0.045 mmol, 72%); mp 109–111 °C; TLC (hexanes/ethyl acetate 1:2) R_f=0.33; $[\alpha]_D^{19}$ +154.4 (*c* 0.06, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2937, 1767, 1653, 1584, 1470, 1444, 1365, 1332, 1273, 1254, 1205, 1188, 1105, 1059; δ_H (300 MHz, $CDCl_3$) 1.55 (3H, d, *J* 6.6, $CHCH_3$), 2.25 (1H, ddd, *J* 18.2, 10.7 and 3.7, $CH_{ax}H$), 2.85 (1H, ddd, *J* 18.2, 2.6 and 2.6, CHH_{eq}), 3.88–3.98 (1H, m, *H*-3), 3.98 (3H, s, OCH_3), 4.52 (1H, dd, *J* 14.2 and 7.2, *CH*HN), 4.73 (1H, dd, *J* 14.2 and 3.1, CH*H*N), 4.83–4.87 (1H, m, *CH*CH_3), 7.29–7.36 (2H, m, Ph*H*), 7.40–7.45 (2H, m, Ph*H*), 7.64 (1H, t, *J* 7.8, Ph*H*), 7.72 (1H, dd, *J* 7.7 and 1.1, Ph*H*), 7.83–7.86 (2H, m, Ph*H*), 7.96 (1H, s, triazole); δ_C (75 MHz, $CDCl_3$) 20.8 (CH_3), 25.3 (CH_2), 53.9 (CH_2), 56.5 (OCH_3), 70.6 (CH), 71.3 (CH), 117.9 (CH), 119.1 (CH), 120.0 (C), 121.0 (CH), 125.7 (2×CH), 128.1 (CH), 128.8 (2×CH), 130.6 (C), 133.8 (C), 134.8 (CH), 138.5 (C), 147.8 (C), 148.0 (C), 159.5 (C), 183.1 (C), 183.5 (C); *m*/*z* (EI^+) 415 (3%, M^+), 270 (4), 255 (5), 241 (6), 229 (13), 213 (5), 197 (6), 171 (6), 152 (7), 145 (10), 128 (15), 116 (51), 103 (38), 89 (48), 77 (49), 63 (45), 55 (52), 41 (100); HRMS (FAB^+, M^+) found 415.1528, calcd for $C_{24}H_{21}N_3O_4$ 415.1532.

Acknowledgements

The authors thank the Royal Society of New Zealand Marsden fund for financial support.

Supplementary data

Full experimental details, NOE data, ^1H and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.048.

References and notes

1. Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.
2. Li, J. W.-H.; Vederas, J. C. *Science* **2009**, *325*, 161.
3. (a) Sperry, J.; Bachu, P.; Brimble, M. A. *Nat. Prod. Rep.* **2008**, *25*, 376; (b) Brimble, M. A.; Nairn, M. R.; Prabaharan, H. *Tetrahedron* **2000**, *56*, 1937; (c) Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rep.* **1999**, *16*, 267.
4. Omura, S.; Tanaka, H.; Koyama, Y.; Oiwa, R.; Katagiri, M.; Awaya, J.; Nagai, T.; Hata, T. *J. Antibiot. (Tokyo)* **1974**, *27*, 363.
5. Tanaka, H.; Koyama, Y.; Awaya, J.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *J. Antibiot. (Tokyo)* **1975**, *28*, 860.
6. Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H.; Omura, S. *J. Antibiot. (Tokyo)* **1975**, *28*, 868.
7. Tanaka, H.; Marumo, H.; Nagai, T.; Okada, M.; Taniguchi, K.; Omura, S. *J. Antibiot. (Tokyo)* **1975**, *28*, 925.
8. Omura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320.
9. Kasai, M.; Shirahata, K.; Ishii, S.; Mineura, K.; Marumo, H.; Tanaka, H.; Omura, S. *J. Antibiot. (Tokyo)* **1979**, *32*, 442.
10. Nakagawa, A.; Fukamachi, F.; Yamaki, K.; Hayashi, M.; Ohishi, S.; Kobayashi, B.; Omura, S. *J. Antibiot. (Tokyo)* **1987**, *40*, 1075.
11. Imai, H.; Suzuki, K.; Miyazaki, S.; Kadota, S. Jap. Patent 61, 152668, **1986**; *Chem. Abstr.* **1986**, *105*, 151548x.
12. Kumazawe, T.; Oshima, E.; Obase, H.; Omori, T.; Shii, H.; Shuto, K. Jap. Patent 61, 152669, **1986**; *Chem. Abstr.* **1987**, *106*, 17030q.
13. Imai, H.; Suzuki, K.; Kadota, S.; Iwanami, M.; Saito, T. *J. Antibiot. (Tokyo)* **1989**, *42*, 1186.
14. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699.
15. Iwai, Y.; Kimura, K.; Takahashi, Y.; Hinotozawa, K.; Shimizu, H.; Tanaka, H.; Omura, S. *J. Antibiot. (Tokyo)* **1983**, *36*, 1268.
16. (a) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128; (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51; (c) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 15366.
17. (a) Gibson, J. S.; Andrey, O.; Brimble, M. A. *Synthesis* **2007**, 2611; (b) Brimble, M. A.; Gibson, J. S.; Sejberg, J. J. P.; Sperry, J. *Synlett* **2008**, 867; (c) Sperry, J.; Gibson, J. S.; Sejberg, J. J. P.; Brimble, M. A. *Org. Biomol. Chem.* **2008**, *6*, 4261; (d) Sperry, J.; Sejberg, J. J. P.; Stiemke, F. M.; Brimble, M. A. *Org. Biomol. Chem.* **2009**, *7*, 2599.
18. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004; (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057; (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
19. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568.
20. (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178; (b) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *19*, 2263; (c) For recent reviews on the Hauser–Kraus annulation see: Rathwell, K.; Brimble, M. A. *Synthesis* **2007**, 643; (d) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892.
21. (a) Shibata, T.; Iiono, K.; Sugimura, Y. *Heterocycles* **1986**, *24*, 1331; (b) Robinson, J. E.; Brimble, M. A. *Org. Biomol. Chem.* **2007**, *5*, 2572.
22. Casas-Solvas, J. M.; Vargas-Berenguel, A.; Capitan-Vallvey, L. F.; Santoyo-Gonzalez, F. *Org. Lett.* **2004**, *6*, 3687.
23. (a) For preparation of the benzyne precursor see: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211; (b) Atkinson, D. J.; Sperry, J.; Brimble, M. A. *Synthesis* **2010**, 911.
24. (a) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461; (b) Shi, F.; Waldo, J.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409.
25. For the preparation of $NaHSO_4$–SiO_2 see: Khalili, M. S.; Ghafuri, H.; Mojahedi-Jahromi, S.; Hashemi, M. H. *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 175.