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Target cum flexibility: an alkyne [2+2+2]-cyclotrimerization strategy for synthesis of trinem library

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ABSTRACT

A rapid access to the central 4,5,6-tricyclic core of 4,5,6-trinems has been achieved by employing the alkyne [2+2+2]-cyclotrimerization as the key and final reaction in the synthesis.

Effective methods that address the complex molecular ensemble and also provide flexibility in modulating the pharmacokinetics are important tools in the modern drug discovery programs.[1] Engagement of the intermolecular (cyclo)additions as the key skeletal constructs at the penultimate stages in a target oriented synthesis will provide enormous versatility for altering the target properties and is one of the ongoing programs in our group.[2] Herein, we exemplify the potential of such an approach by selecting the *trinem* skeleton as a target and the key bicycloannulation as the final step. Tricyclic β-lactam antibiotics, referred to as trinems, are a new class of broad spectrum antibacterial agents.[3] When compared with conventional carbapenems, trinems have good resistance to beta-lactamases and dehydropeptidases and offer superior stability in the stomach and intestine.[4] A handful of non-conventional fused polycyclic β-lactams have been described with interesting anti-bacterial activities (Fig. 1).

In this context, various approaches for cycloannulations on the β-lactam have been documented among which the ring-closing metathesis (RCM) approach has been employed by several groups.[5] Our attention has been drawn to the 6-(1-hydroxyethyl)-cyclonocardicin developed by the researchers at Merck.[6] This benzannulated trinem has shown promising activity against a wide range of pathogens including both Gram positive (*Staphylococcus aureus*, *Strep. pyogenes*, *Bacillus subtilis*) and Gram negative (*Escherichi coli*, *Pseudomonas*, *Proteus morgani*, etc.) and thus is a potential lead for further exploration in anti-bacterial therapeutics. We have been interested in providing a strategy which should facilitate the placement of a wide range of functional groups and appendages on the aromatic ring without diverting from the original target oriented route. Keeping this in mind, the central trinem skeleton has been disconnected so as to employ trimerization as the key reaction.[7–9] Since the cyclotrimerization was planned as the final step, this strategy should effectively address a rapid synthesis of the trinem library as various alkynes are commercially available and are easy to synthesize. In order to investigate in this direction, the diynes **1**–**3** were selected as the model substrates to check the feasibility of this approach and also to understand the substituent influence on the regioselectivity.[10]

Synthesis of diynes **1**–**3** was started with the optimization of the conditions for the addition of an alkynyl anion at the C(4)-position of 4*AA* to prepare the intermediate alkynes **5**–**7**. The alkyne **5** has been prepared earlier via the addition of lithiated trimethylsilyl acetylene followed by desilylation.[11] To have a simple and practical method for accessing the alkynes on large scales, we opted for the addition of alkynyl Grignard reagents. After substantial optimization of the reaction conditions, the ethylnylmagnesium chloride (generated by passing dry acetylene gas to a

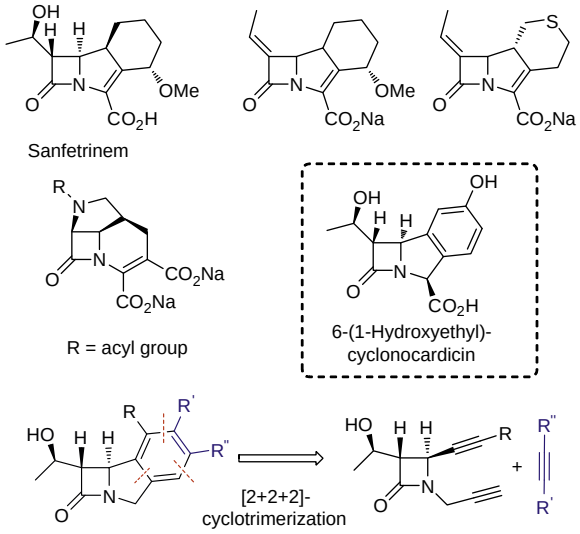

Figure 1. Some tricyclic β-lactam antibiotics and proposed cyclotrimerization approach for benzannulated 4,5,6-trinems.

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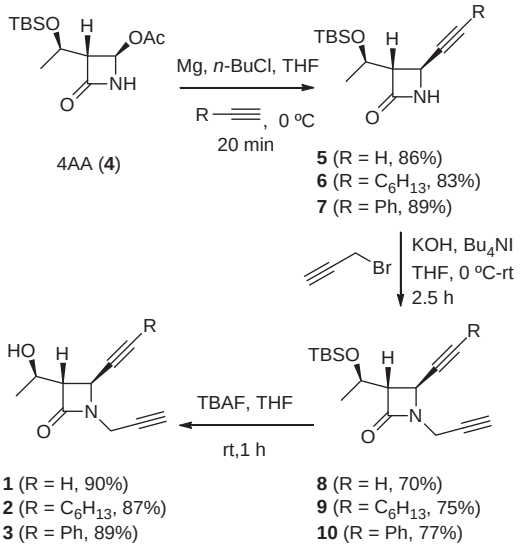
solution of preformed *n*-BuMgCl in THF) was added to azetidin-2-one **4** to get **5** in excellent yield. Under similar conditions by using 1-octyne and phenyl acetylene, the other two alkynyl azeditines **6** and **7** have been prepared in very good yields and on multigram scales. The *N*-propargylation of compounds **5**–**7** was carried out by using propargyl bromide and KOH in the presence of *n*-Bu_4NI in THF to afford the corresponding diynes **8**–**10** which were subsequently treated with TBAF to provide the final diynes **1**–**3** (Scheme 1).[5c]

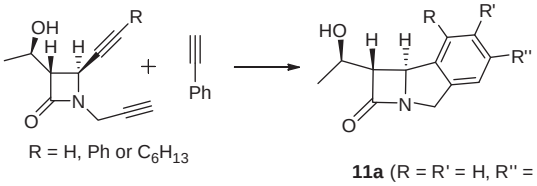
Using phenyl acetylene as a substrate, the feasibility of cyclotrimerization of the diynes **1**–**3** has been examined by screening available Rh- and Ru-based catalysts. With the simple diyne **1**, the reaction was facile with Wilkinson's catalyst (A).[12] The two regio-isomeric trinems **11a**/**11b** were formed in equal proportions. A marginal improvement in the product yields could be seen when the catalysts $Cp^*RuCl(cod)$ (B)[13] and $[Rh(cod)_2]BF_4$/(*R*)-BINAP (C)[14] were employed, albeit without any substantial improvement in the regioselectivity.[10] The cyclotrimerization of the mono-substituted diynes **2** and **3** with phenyl acetylene were not facile with Wilkinson's catalyst. When the catalysts B and C were employed, the reactions proceeded smoothly at rt and gave the corresponding trinems (Table 1) in good yields. The trimerization of *n*-hexyl substituted diyne **2** gave mainly the 1,3-isomer **12a**. The product distribution was independent of the catalyst employed. With the phenyl substituted diyne **3**, the trimerization gave exclusively the 1,3-product **13a**. The regioselectivity noticed with the trimerization of diynes **2** and **3** endorse them for further exploration in constructing the homochiral trinem libraries. The attempted cyclotrimerization reactions of the alkynes **1–3** with symmetrically disubstituted akynes bis-(trimethylsilyl)acetylene, dimethyl acetylenedicarboxylate, and diphenylacetylene met with failure. With 2-butyne-1,4-diol as a substrate, the requisite trimerization product **14**[15] from the cyclotrimerization of the diyne **1** could be obtained only with the Wilkinson's catalyst. But with the diynes **2** and **3**, none of the three catalysts resulted in the trimerziation product.

With the optimized catalyst and conditions of the cyclotrimerization reactions with phenylacetylene, next we did proceed with the synthesis of a small collection of trinems by employing easily available alkynes as the co-partners for the cyclotrimerization. Tables 1 and 2 show the versatility of our strategy. The cyclotrimerization reactions of diyne **1** were carried out by employing the Wilkinson's catalyst. The reaction with acetylene was conducted in a sealed tube at 80 °C (entry 15, Table 2). With a wide range of terminal alkynes employed, the requisite cyclotrimerization products were obtained in good to excellent yields, however, as 1:1 inseparable regiomeric mixture. For the structural analysis, compounds **16a**,[16] **18b**,[17] and **19b**[18] were separated by preparative TLC and their constitutions were confirmed with the help of extensive 2D NMR experiments. For example, a combination of observations obtained from NOESY, HSQC, and HMBC studies helped to deduce the structure of compound **19b**. The proton resonating at 7.23 ppm as a singlet was found to be connected to the aromatic carbon C(8) in HSQC. In HMBC, correlations were observed between C(8)–H and C(12) (38.8 ppm). The C(12)–H appeared as a triplet at 3.87 ppm and showed cross peaks with C(8) (124.1 ppm) and C(10) (129.0 ppm). There was no connectivity observed between C(11) (123.1 ppm) and C(12)–H. This confirmed the position of the side chain to be at C(9). The through-space



Scheme 1. Synthesis of diynes **1**–**3**.

Table 1
Examination of the cyclotrimerization reaction of diynes **1**–**3** with phenylacetylene



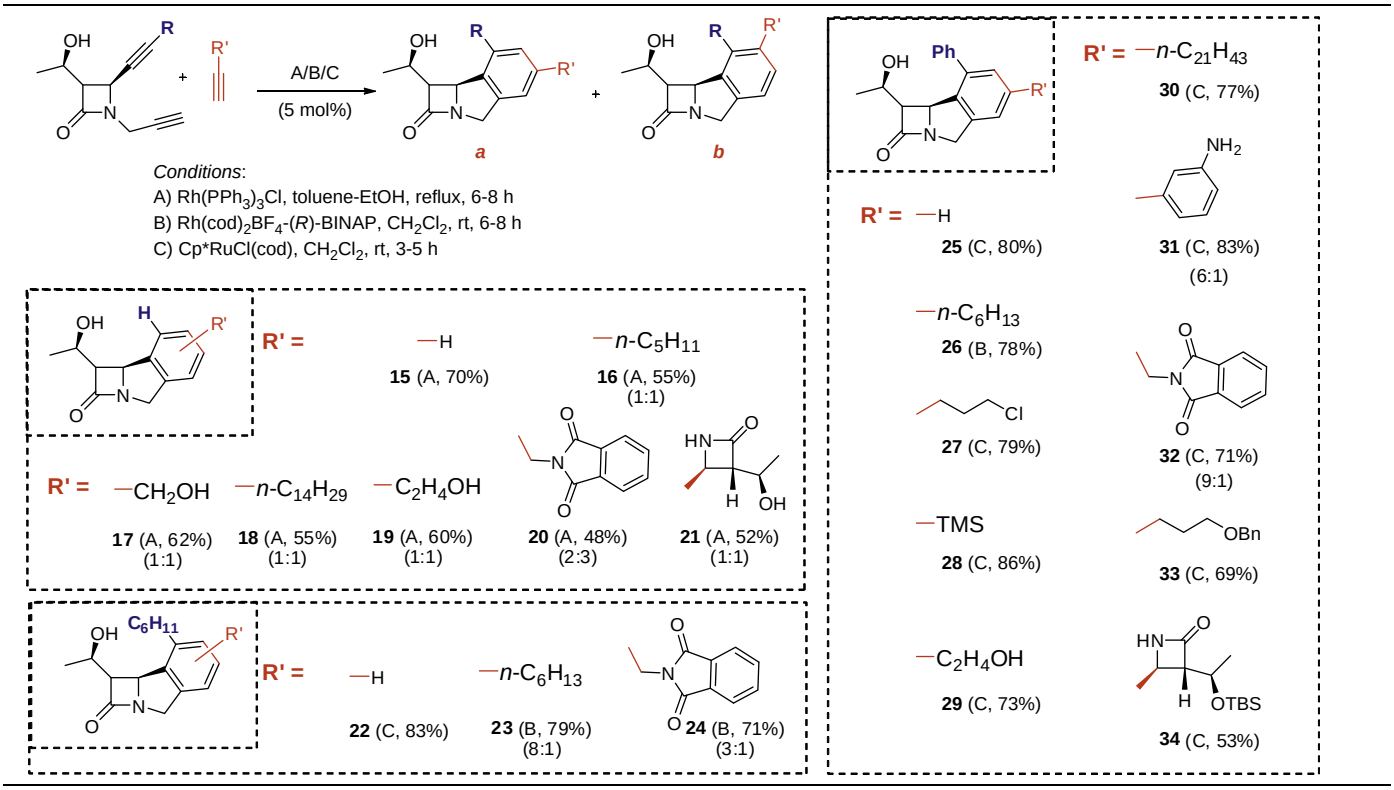
Catalyst and *Conditions*:

A) $Rh(PPh_3)_3Cl$ (5 mol%), toluene-EtOH
B) $Rh(cod)_2BF_4$-(*R*)-BINAP, (5 mol%), CH_2Cl_2
C) Cp*RuCl(cod) (5 mol%), CH_2Cl_2

11a (R = R' = H, R'' = Ph)
11b (R = R''= H, R' = Ph)
12a (R= $^nC_6H_{13}$, R' =H, R'' = Ph)
13a (R = R'' = Ph, R' = H)

Entry	Diyne	R=	Method	Temp/time (°C/h)	Product(s)	a:b	Yield (%)
1	1	H	A	80/12	**11a**, **11b**	1:1	64
2	1	H	B	rt/7	**11a**, **11b**	1:1	68
3	1	H	C	rt/4	**11a**, **11b**	1:1	80
4	2	*n*-C_6H_{13}	A	80/18	**12**	–	No reaction
5	2	*n*-C_6H_{13}	B	rt/7	**12**	–	78
6	2	*n*-C_6H_{13}	C	rt/4	**12**	–	–
7	3	Ph	A	80/24	**13**	–	No reaction
8	3	Ph	B	rt/7	**13**	–	80
9	3	Ph	C	rt/4	**13**	–	81

Table 2
Scope of cyclotrimerization reaction of diynes **1**–**3**



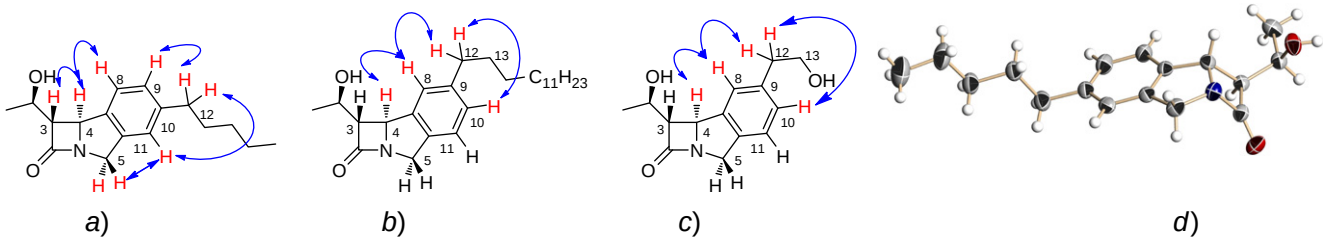


Figure 2. Observed through spatial contacts in the NOESY spectra of compounds (a) **16a**, (b) **18b**, (c) **19b** and (d) ORTEP structure of compound **16a**.

connectivity observed between C(8)–H and C(12)–H in the NOESY spectrum further substantiated the assigned regiochemistry. In similar lines, the structure of the compound **16a** was confirmed by NOE studies. For example, the C(4)–H showed through spatial interactions with both the C(8)–H and C(5)–H. The C(5)–H gave an additional NOE signal with C(11)–H. In addition, the cross peaks between C(12)–H/C(9)–H and C(12)–H/C(11)–H, and the absence of cross peak between C(12)–H/C(8)–H confirmed the attachment of alkyl side chain to C(10) carbon (Fig. 2b). Due to the aniosotrpic deshielding effect of the lactam carbonyl, the diastereotropic methylene protons C(5) were well separated (ca. 0.8 ppm).[5c] The single crystal X-ray crystallographic studies of **16a** (Fig. 2d) further confirmed the assigned structure.[19–21] Some of the representatives through-space interactions noticed in the NOE spectrum of compound **19b** have been presented in Figure 2c.

The scope of the cyclotrimerization reactions with the substituted diynes **2** and **3** was next explored. With terminal alkynes, the cyclotrimerization of diynes **2** and **3** was achieved smoothly at rt. The regioselectivity was excellent with the diyne **3** trimerizations. In case of diyne **2**, along with the anticipated 1,3-regiomer, the 1,2-isomer was also obtained as a minor product. A variety of terminal alkynes have been employed for the cyclotrimerization with diyne **3**. Various functional groups are tolerant under the reaction conditions. The products **27** and **31** obtained from the cyclotrimerization of diyne **3** with 5-chloropent-1-yne and 3-ethynylaniline are quite attractive, as these products provide a suitable functional group handle for further diversification with simple chemical maneuvering.

In summary, a [2+2+2] alkyne cyclotrimerization reaction was employed successfully to construct the central 4/5/6 tricyclic framework of 6-(1-hydroxyethyl)-cyclonocardicin trinems. Introduction of different substituents to the structure was achieved easily by simply employing a suitable alkyne at the final event of bicyclo-annulation, and thus are allowed to prepare a focussed library of trinem like small molecules easily. Further studies toward the synthesis of carboxylate appended trinems and ring size modifications are in progress. Their synthesis and the biological activities will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H, ^{13}C DEPT, MS and 2D NMR Spectra of selected compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.123.

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15. *Spectral data of compound* **14**: Yellow color oil, yield: 65%; $[\alpha]_D^{25}$: −19.8 (*c* 0.6, MeOH); IR ($CHCl_3$) *v*: 3397, 3340, 2925, 2855, 2724, 1756, 1560, 1463, 1376, 1256, 1187, 1168, 1139, 1076, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 1.30 (d, *J* = 6.3 Hz, 3H), 3.01 (dd, *J* = 2.3, 6.5 Hz, 1H), 4.05 (d, *J* = 14.5 Hz, 1H), 4.13–4.16 (m, 1H), 4.60 (s, 2H), 4.63 (s, 2H) , 4.79 (d, *J* = 14.5 Hz, 1H), 4.85 (s, 1H), 5.05 (br s, 2H), 5.14 (br s, 1H), 7.33 (s, 1H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 20.4 (q), 49.8 (t), 58.4 (d), 59.5 (t, 2C), 62.9 (d), 66.0 (d), 120.2 (d), 120.8 (d), 137.1 (s), 137.9 (s), 138.0 (s), 139.0 (s), 177.6 (s) ppm; ESI-MS *m*/*z*: 286.1 (46%, [M+Na]$^+$). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.88; H, 6.37; N, 5.37.
16. *Spectral data of compound* **16a**: Colorless needles, yield: 55%; $[\alpha]_D^{25}$: 28.5 (*c* 1, $CHCl_3$); IR ($CHCl_3$) *v*: 3404, 3019, 2960, 2859, 2400, 1752, 1618, 1457, 1332, 1160, 1135, 1045, 929, 881 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.29–1.37 (m, 4H), 1.42 (d, *J* = 6.3 Hz, 3H), 1.60 (quintet, *J* = 7.8 Hz, 2H), 2.15 (br s, 1H), 2.61 (t, *J* = 7.6 Hz, 2H), 3.15 (dd, *J* = 2.4, 5.9 Hz, 1H), 4.08 (br d, *J* = 14.6 Hz, 1H), 4.34 (quintet, *J* = 6.3 Hz, 1H), 4.84–4.89 (m, 2H), 7.05 (s, 1H), 7.12 (br d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 21.8 (q), 22.5 (t), 31.3 (t), 31.4 (t), 35.7 (t), 51.8 (t), 59.7 (d), 65.4 (d), 67.1 (d), 122.9 (d), 123.2 (d), 128.3 (d), 136.9 (s), 142.5 (s), 143.3 (s), 179.0 (s); ESI-MS *m*/*z*: 274.1 (45%, [M+H]$^+$); 296.0 (40%, [M+Na]$^+$), 312.0 (30%, [M+K]$^+$). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.48; H, 8.45; N, 5.23.
17. *Spectral data of compound* **18b**, Thick liquid, yield: 55%; $[\alpha]_D^{25}$: −18.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) *v*: 3406, 3019, 2927, 1757, 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.25–1.32 (m, 22H), 1.42 (d, *J* = 6.3 Hz, 3H), 1.59 (quintet, *J* = 7.2 Hz, 2H), 1.96 (br s, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 3.16 (dd, *J* = 2.5, 6.2 Hz, 1H), 4.07 (br d, *J* = 14.4 Hz, 1H), 4.34 (quintet, *J* = 6.2 Hz, 1H), 4.83–4.87 (m, 2H) , 7.09–7.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 22.0 (q), 22.7 (t) , 29.4 (t, 2C) , 29.5 (t) , 29.6 (t) , 29.7 (t, 5C), 31.7 (t) , 31.9 (t) , 35.8 (t) , 51.7 (t) , 59.9 (d), 65.5 (d), 67.1 (d), 122.8 (d), 123.3 (d), 128.4 (d), 139.6 (s), 139.8 (s), 143.2 (s), 178.8 (s); ESI-MS *m*/*z*: 400.4 (8%, [M+H]$^+$), 422.4 (100%, [M+Na]$^+$). Anal. Calcd for $C_{26}H_{41}NO_2$: C, 78.15; H, 10.34; N, 3.51. Found: C, 78.28; H, 10.57; N, 3.34.
18. *Spectral data of compound* **19b**: Colorless oil, yield: 60%; $[\alpha]_D^{25}$: −26.2 (*c* 1, $CHCl_3$); IR ($CHCl_3$) *v*: 3422, 3018, 2932, 1752, 1457, 1330, 1044, 928 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (d, *J* = 6.3 Hz, 3H), 1.88 (br s, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 3.18 (dd, *J* = 2.4, 6.3 Hz, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 4.07 (dd, *J* = 2.2, 14.2 Hz, 1H), 4.34 (quintet, *J* = 6.3 Hz, 1H), 4.84–4.91 (m, 2H), 7.18 (s, 1H), 7.23 (s, 1H), 7.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9 (q), 38.8 (t), 51.6 (t), 59.9 (d), 63.5 (t), 65.4 (d), 67.1 (d), 123.1 (d), 124.1 (d), 129.0 (d), 138.8 (s), 140.1 (s), 140.5 (s), 178.8 (s) ppm; ESI-MS *m*/*z*: 246.9 (9%, [M+H]$^+$), 269.9 (10%, [M+Na]$^+$). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.19; H, 6.67; N, 5.39.
19. X-ray intensity data of compound **16a** was collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα = 0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997)[20] was used for structure solution and full-matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.
20. Sheldrick, G. M. SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997.
21. The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 791182. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road,Cambridge CB2 1EZ, UK [fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk].