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The Synthesis of Enantiomerically Pure *(2R)*-α-Methylisoserine.

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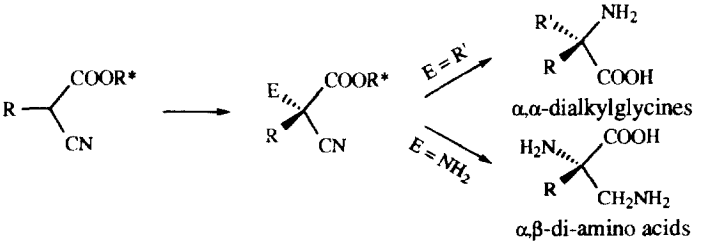
Abstract: The title compound was prepared by diastereoselective methylation of chiral *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl acetoxycyanoacetate and subsequent nitrile hydrogenation.

The β-aminoalcohol functionality associated with a carboxylic group is present in a large number of biologically active compounds such as carnitine,[1] GABOB,[2] statine and their analogues,[3] taxol,[4] etc. At present we are interested in the synthesis of novel and interesting α,α-disubstituted amino acids and as a part of our program on the synthesis of α-methyl amino acids we were faced with the problem of developing an efficient synthesis of optically pure α-methylisoserine.

Earlier studies in this laboratory have shown that lithium enolates derived from chiral α-cyanoesters have a tendency to undergo highly diastereoselective trapping with some electrophiles, this has allowed us to develop a general protocol for the synthesis of homochiral α,α-disubstituted amino acids which has been successfully applied to the synthesis of isovaline,[5] α-methylphenylalanine,[6] α-methyltryptophan,[7] α-methyldiphenylalanine,[8] and α-methylvaline[9] using reactive alkyl halides as electrophiles and also to the synthesis of α,β-di-amino acids[10] using O-(diphenylphosphinyl)hydroxylamine as the electrophile. (Scheme 1)

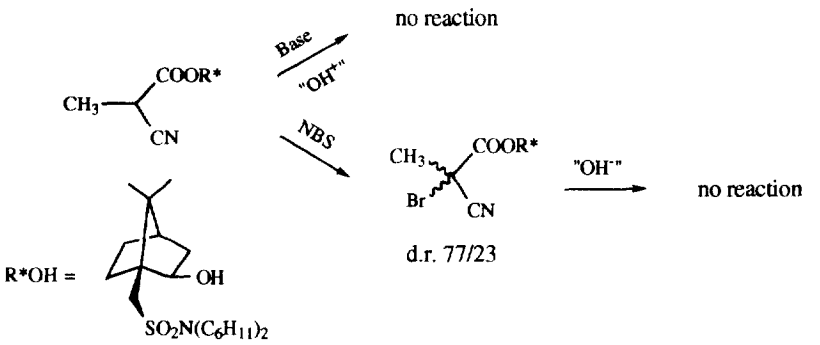


Scheme 1

Thus, we have attempted to use this approach in the synthesis of enantiomerically pure α-methylisoserine and a logical disconnection would be the diastereoselective electrophilic hydroxylation of chiral *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate. This substrate possesses the required substituents necessary to generate the desired α-methylisoserine, after hydroxylation, by hydrogenation of the nitrile and

hydrolysis of the ester. First of all, *trans* -2-phenylsulfonyl-3-phenyloxaziridine, which has proven synthetic utility in the direct oxidation of enolates,[11] was chosen to introduce the desired hydroxyl group in the α-position.

Submission of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate to alkaline hexamethyldisilazides or potassium carbonate and *trans* -2-phenylsulfonyl-3-phenyloxaziridine did not give the desired hydroxylated compound but an unidentified compound. Alternatively, we tried α-acetoxylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate by reaction with lithium di-isopropylamide to generate the enolate and subsequent treatment with lead tetra-acetate according to the method described by Oppolzer and Dudfield[12] for the asymmetric α-acetoxylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl carboxylic esters. However, this protocol also failed to give the desired hydroxylated compound, and we recovered unreacted starting material.



Scheme 2

As has been described previously,[13] bromine can be easily replaced by an hydroxyl group in related 2-bromo-2-cyanoglycines, and thus we tried this approach in the synthesis of α-methylisoserine. Bromination of *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate with NBS afforded the desired α-bromo compound in 91 % yield and with a moderate steroselectivity (d. r. = 77/23) although both diastereoisomers could be easily isolated by column chromatography. Subsequent reaction of the α-bromo compound with sodium acetate in DMF or tributyltin methoxide did not allow us to perform nucleophilic replacement of the bromine atom. Alternatively, treatment of the α-bromo compound with benzoylperoxide as a radicalophile, according to the literature procedure for the α-benzoyloxylation of 2-bromo-*N*-benzoylglycine,[14] afforded a mixture of unidentified compounds.

As we were unable to introduce the hydroxyl group in the α-position we decided to change our synthetic strategy and we tested the insertion of a methyl group into the chiral α-acetoxycyanoacetate **1**. This starting material was easily obtained in a five-step procedure, without isolation of any intermediate, from bromoacetyl bromide in 62 % overall yield.

Having prepared the starting α-acetoxy compound, the next step was α-methylation. Submission of **1** to lithium di-isopropylamide and subsequent enolate trapping with methyl iodide under normal conditions only afforded decomposition by-products, so we tried this reaction in different bases to generate the enolate and we

obtained the following results. When we used sodium methoxide in methanol as base *(1S,2R,4R)*-10-dicyclohexylsulfamoylisoborneol was isolated from the reaction mixture. The use of potassium *tert*-butoxide as base or alkylation under phase transfer conditions (sodium hydroxide/tetrabutylammonium hydrogen sulphate) led to complex mixtures in which the desired alkylation product could only be isolated in low chemical yield. Finally, *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-acetoxycyanoacetate **1** was treated with potassium carbonate in the presence of methyl iodide and under these conditions we obtained a 92 % yield of the desired *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-acetoxy-2-cyanopropanoate **2** as a mixture of diastereoisomers (d. r. = 77/23) from which the major compound can be easily isolated in 71 % yield by flash chromatography in a silica gel column using ether/hexane 1:1 as eluent.

The diastereomeric ratio of the products was determined from the crude reaction spectra by integration of the ^{1}H NMR (300 MHz) absorptions of the methine proton of the esters, as each diastereoisomer in the pair gave a doublet of doublets at about 5 ppm for the major compound and 4.9 ppm for the minor compound.

The absolute configuration of the newly-formed stereogenic centre was assigned by single crystal X-ray analysis and showed the *R* configuration at C(2). (Figure 1)

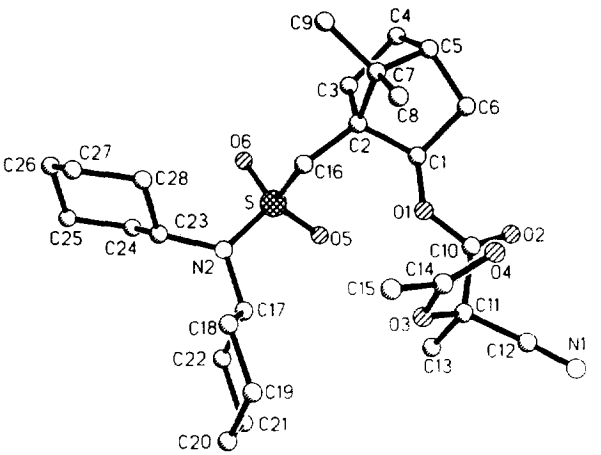
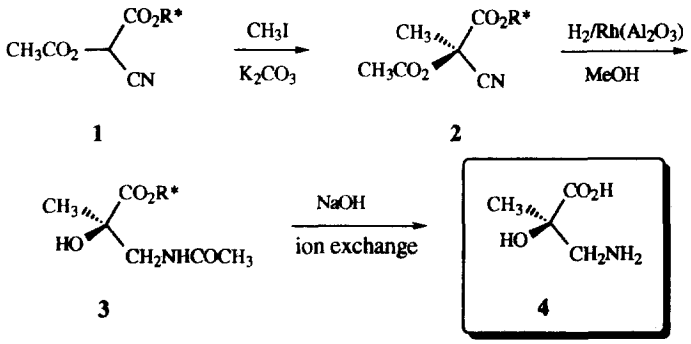


Figure 1

Hydrogenation of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-acetoxy-2-cyanopropanoate **2** with rhodium on alumina at room temperature and atmospheric pressure cleanly afforded a single product whose spectroscopical data were not in accordance with the expected hydrogenation product. This compound was identified as *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-acetamido-2-hydroxy-2-methylpropanoate **3** and was formed from hydrogenation of cyanoester **2** and subsequent migration of the acetyl protecting group from the hydroxyl to the newly formed amino group. Hydrolysis of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-acetamido-2-hydroxy-2-methylpropanoate **3** with NaOH furnished the corresponding potassium salts of the α-hydroxy-β-amino acid in enantiomerically pure form, from which we obtained the free amino acid **4** by ion exchange chromatography.



Scheme 3

To conclude, electrophilic methylation of chiral enolates derived from *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl acetoxycyanoacetate **1** allowed us to obtain enantiomerically pure *(2R)*-α-methylisoserine **4**, a new synthetic α-hydroxy-β-amino acid. Further studies on the incorporation of amino acid **7** into peptides, changes induced in the peptide properties due to the presence of the α-hydroxy-β-amino acid moiety and the specific properties of this compound are being undertaken and will be published in due course.

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EXPERIMENTAL

Apparatus: Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241-C polarimeter with a thermally-jacketed 10 cm cell at 25°C. IR spectra were obtained on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform or deuterated water and referenced with respect to the residual solvent signal on a Varian Unity 300 or a Bruker AMX300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants *(J)* are measured in Hertz. Elemental analyses were performed on a Perkin-Elmer 200 C,H,N,S elemental analyser.

Chemicals: All reactions were carried out under argon with magnetic stirring. Solvents were dried prior to use. All reagents were purchased from the Aldrich Chemical Co. and used as received. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was undertaken on silica gel (Kiesegel 60).

***(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl acetoxycyanoacetate 1.** Bromoacetyl bromide (2.02 g, 10 mol) was added by means of a syringe to a stirred mixture of silver cyanide (1g, 7.5 mmol) and *(1S,2R,4R)*-10-dicyclohexylsulfamoylisoborneol (2 g, 5 mmol) in toluene (60 ml) under argon and the mixture was heated at 80 °C for 1 h. The reaction mixture was then filtered, washed successively with a 10% aqueous sodium hydrogen carbonate solution and water, dried with magnesium sulphate and concentrated *in vacuo* to afford the crude *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl bromoacetate which was dissolved in acetonitrile (20 ml). Then silver nitrate (1.2 g, 7 mmol) was added and the mixture stirred at 60 °C for 24 h and concentrated *in vacuo* at 30 °C. The resulting residue was treated with ether (100 ml) and the solid

silver bromide, removed by filtration and thoroughly washed with ether. The combined organic layers were washed with water, dried with magnesium sulphate and concentrated *in vacuo* to afford the crude *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl nitro-oxiacetate. A mixture of the crude *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl nitro-oxiacetate and sodium acetate trihydrate (0.7 g, 5 mmol) dissolved in dimethylsulphoxide (10 ml) was stirred at room temperature for 1h and then poured into brine (40 ml) at 0 °C. The solution was extracted with ether three times and the combined organic layers were washed with brine, dried with magnesium sulphate and concentrated *in vacuo*. The resulting liquid was filtered through silica gel (ether as eluent), the eluate was evaporated and the residue dissolved in ethanol (50 ml). Then trimethylsilyl cyanide (0.75 ml, 6 mmol) was added by means of a syringe and the reaction was stirred for 30 min at room temperature. The reaction mixture was treated with 20 ml of a saturated aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane. The organic layers were dried with magnesium sulphate and the solvent evaporated under reduced pressure. The resulting residue containing the crude cyanohydroxyacetate was used as such in the next step. Acetyl chloride (785 mg, 10 mmol) was added by means of a syringe to a stirred mixture of silver cyanide (1g, 7.5 mmol) and the crude *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl cyanohydroxyacetate in toluene (60 ml) under argon and the mixture was heated at 80 °C for 5 h. The reaction mixture was then filtered, washed successively with a 10% aqueous sodium hydrogen carbonate solution and water, dried with magnesium sulphate and concentrated *in vacuo*. The residue was then purified by flash chromatography in a silica gel column using ether/hexane 1:2 as an eluent to afford 1.62 g (62 % overall yield) of pure *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl acetoxycyanoacetate as a white solid. IR (Nujol) 2252, 1759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) of the mixture: δ 0.86 (s, 3H), 0.98 and 1.04 (s, 3H), 1.02-2.00 (m, 27H), 2.19 and 2.20 (s, 3H), 2.60 and 2.65 (d, 1H, J = 13.5), 3.17-3.35 (m, 2H), 3.22 and 3.23 (d, 1H, J = 13.5), 5.04 and 5.29 (dd, 1H, J = 7.5, J = 3.6 and J = 7.8, J = 3), 5.71 and 5.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) of the mixture: δ 19.57 and 19.68, 19.83 and 20.08, 20.10, 25.02, 26.03 and 26.17, 26.24 and 26.75, 30.36 and 30.50, 32.06 and 32.59, 32.73 and 33.20, 38.64, 44.17 and 44.30, 49.10 and 49.19, 49.70 and 49.91, 53.59 and 53.88, 57.24 and 57.54, 59.05 and 59.12, 81.07 and 82.05, 112.55 and 112.67, 159.76 and 160.07, 168.01 and 168.19. Anal. Calcd for $C_{27}H_{42}N_2O_6S$: C, 62.04; H, 8.10; N, 5.36; S, 6.13. Found: C, 62.41; H, 8.09; N, 5.57; S, 6.27.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-acetoxy-2-cyanopropanoate 2.** Potassium carbonate (2.1 g , 15 mmol) was added to a well-stirred solution of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-acetoxycyanoacetate **1** (1.56 g, 3 mmol) and methyl iodide (2.15 g, 15 mmol) in dry acetone (60 ml). The resulting mixture was stirred at room temperature for 3h and then filtered and the solid washed with ether. The combined organic layers were concentrated *in vacuo* and the residue was dissolved in ether, washed with water, dried with magnesium sulphate and concentrated *in vacuo*. Purification of the residue by flash chromatography in a silica gel column using ether/hexane 1:1 as an eluent afforded 1.14 g (71 % yield) of diastereomerically pure *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-acetoxy-2-cyanopropanoate **2** as a white solid. M. p. 179 °C; $[\alpha]^D$ = - 25.5 (c, 1 in chloroform), IR (Nujol) 2252, 1751, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (s, 3H), 0.92 (s, 3H), 1.02-2.10 (m, 27H), 1.99 (s, 3H), 2.13 (s, 3H), 2.61 (d, 1H, J = 13.5), 3.22 (d, 1H, J = 13.5), 3.24-3.40 (m, 2H), 5.01 (dd, 1H, J = 7.8, J = 3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.7, 20.0, 20.4, 23.8, 25.2, 26.3, 26.3, 26.9, 29.7, 30.3, 32.2, 33.4, 39.0, 44.3, 49.1, 49.6, 53.3, 57.3, 69.6, 81.9, 115.9, 163.9, 168.4. Anal. Calcd for $C_{28}H_{44}N_2O_6S$: C, 62.66; H, 8.26; N, 5.22; S, 5.97. Found: C, 62.16; H, 8.38; N, 5.45; S, 6.05.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 3-acetamido-2-hydroxy-2-methylpropanoate 3.** A solution of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-acetoxy-2-cyanopropanoate **2** (1.07 g, 2 mmol) in methanol (20 ml) was hydrogenated with rhodium on alumina (500 mg) at 25 °C and atmospheric pressure with vigorous shaking. The reaction was followed by TLC and when it was finished (after 24 h), the catalyst was removed by filtration and the filtrate evaporated to dryness. Purification of the residue by flash chromatography (ether as eluent) afforded 886 mg (82 % yield) of diastereomerically pure *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-acetamido-2-hydroxy-2-methylpropanoate **3** as a white solid. M. p. 171 °C; $[\alpha]^D$ = + 15.9 (c, 1 in chloroform), IR (Nujol) 3361, 1726, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (s, 3H), 0.96 (s, 3H), 1.00-2.10 (m, 27H), 1.37 (s, 3H), 1.94 (s, 3H), 2.65 (d, 1H, J = 13.5), 3.00 (dd, 1H, J = 13.8, J = 4.5), 3.10-3.25 (m, 2H), 3.20 (d, 1H, J = 13.5), 4.01 (dd, 1H, J = 13.8, J = 8.4), 4.85 (dd, 1H, J = 7.8, J = 3), 6.93 (dd, 1H, J = 8.4, J = 4.5); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.9, 20.3, 23.3, 25.0, 26.3, 26.4, 26.9, 31.0, 32.1, 33.4, 40.0, 44.3, 48.7, 49.4, 54.4, 57.8, 75.9, 79.9, 80.0, 172.5, 173.6. Anal. Calcd for $C_{28}H_{48}N_2O_6S$: C, 62.19; H, 8.95; N, 5.18; S, 5.93. Found: C, 61.98; H, 9.03; N, 5.37; S, 5.79.

***(2R)*-2-Methylisoserine 4.** *(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 3-acetamido-2-hydroxy-2-methylpropanoate **3** (810 mg, 1.5 mmol) was added to a 10 % solution of sodium hydroxide in methanol (30 ml) and the mixture was stirred at room temperature for 5h. After completion, the resulting solution was cooled and the solvent evaporated. The residue was diluted in water (30 ml) and washed with ether. The aqueous layer was then refluxed for 20 h. After filtration and extraction with ether the solution was acidified and applied to an ion exchange column (DOWEX® 50 x 8-200, H^+ form, 50 ml). The column was washed with water until the eluate became neutral and then eluted with 5 % aqueous ammonia until the ninhydrin test became negative. The combined eluates were evaporated to dryness to afford 103 mg (58 % yield) of enantiomerically pure *(2R)*-2-methylisoserine **4** as a white solid. M. p. 227 °C; $[\alpha]^D$ = - 11.2 (c, 1 in water); ^1H NMR (D_2O, 300 MHz): δ 1.23 (s, 3H), 2.92 (d, 1H, J = 12.9), 3.10 (d, 1H, J = 12.9); ^{13}C NMR (D_2O, 75 MHz): δ 22.0, 45.1, 71.4, 178.0. Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.52; H, 7.53; N, 11.89.

Single crystal X-ray diffraction analysis of 2.[15] Crystallographic measurement was carried out at ambient temperature on a 4-circle Siemens P4 diffractometer using graphite monochromated molybdenum *Kα* X-radiation (λ = 0.71069 Å) One equivalent set of data was collected in the range $0°<2\theta<50°$ using $\omega/2\theta$ scans. No significant variation was observed in the intensity of the three standard reflections. Lorentz and polarisation corrections were applied to the data-set. The structure was solved by direct methods using SHELXS-86[16] and was refined by full-matrix least squares (based on F^2) using SHELXL-93[17] which used all data for refinement. The weighting scheme was $\omega = [\sigma^2 (F_o^2) + (0.0598P)^2]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions. $C_{28}H_{44}N_2O_6S$, 0.52 x 0.4 x 0.34 mm, M_t = 536.7, orthorhombic, space group $P2_12_12_1$, a = 10.307(2), b = 14.577(2), c = 20.206(3)Å, V = 3035.9(9) $Å^3$, Z = 4, ρ_{calc} = 1.174 g cm^{-3}, $F(000)$ = 1160, , μ = 1.5 cm^{-1}. 3594 independent reflections measured. Final R = 0.0863, ωR = 0.1316 for all independent reflections, R = 0.0491, ωR = 0.1117 for 2488 observed reflections with $F_0 > 4\sigma F_0$.

Non-hydrogen atom co-ordinates (x 10^4) and equivalent isotropic thermal parameters (Å^2 x 10^3) for **2** with standard deviations in parentheses. (U_{eq} is defined as one third of the trace of the orthogonalised U_{ij} tensor.)

Atom	x	y	z	U(eq)
S	2209(1)	1024(1)	5590(1)	47(1)
O(1)	3193(3)	2765(2)	6833(2)	42(1)
O(2)	3585(3)	4278(2)	6698(2)	70(1)
O(3)	5644(3)	2363(2)	7073(2)	45(1)
O(4)	4914(4)	2925(2)	8037(2)	66(1)
O(5)	2782(4)	1865(2)	5374(2)	63(1)
O(6)	996(3)	727(2)	5308(2)	63(1)
N(1)	6839(4)	4523(3)	7289(2)	72(1)
N(2)	3247(4)	201(2)	5470(2)	48(1)
C(1)	1820(4)	2889(3)	6656(2)	43(1)
C(2)	1146(4)	1949(3)	6676(2)	43(1)
C(3)	-134(4)	2118(4)	6272(3)	59(1)
C(4)	-939(5)	2741(4)	6748(3)	74(2)
C(5)	-61(5)	2842(3)	7352(3)	63(1)
C(6)	1051(5)	3474(3)	7158(3)	62(1)
C(7)	605(5)	1892(3)	7402(2)	51(1)
C(8)	1647(5)	1838(4)	7941(2)	65(1)
C(9)	-335(6)	1090(4)	7523(3)	82(2)
C(10)	3942(5)	3507(3)	6781(2)	47(1)
C(11)	5382(4)	3233(3)	6768(2)	43(1)
C(12)	6179(4)	3967(3)	7074(2)	48(1)
C(13)	5732(5)	3130(4)	6036(2)	63(1)
C(14)	5347(5)	2292(3)	7726(3)	50(1)
C(15)	5628(6)	1349(3)	7978(3)	74(2)
C(16)	1960(4)	1125(3)	6461(2)	42(1)
C(17)	4664(4)	404(3)	5551(2)	52(1)
C(18)	5277(5)	-106(4)	6118(3)	68(2)
C(19)	6713(5)	132(5)	6194(3)	86(2)
C(20)	7447(5)	-30(5)	5557(4)	94(2)
C(21)	6841(6)	492(5)	4994(4)	90(2)
C(22)	5390(6)	266(4)	4908(3)	72(2)
C(23)	2842(5)	-767(3)	5363(2)	51(1)
C(24)	2240(6)	-940(4)	4690(2)	72(2)
C(25)	1971(6)	-1957(4)	4581(3)	83(2)
C(26)	1165(8)	-2338(4)	5127(4)	107(3)
C(27)	1764(8)	-2187(4)	5794(3)	94(2)
C(28)	2028(6)	-1167(3)	5917(2)	66(2)

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