Natural Products

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Diastereoselective Total Synthesis of (±)-Schindilactone A**

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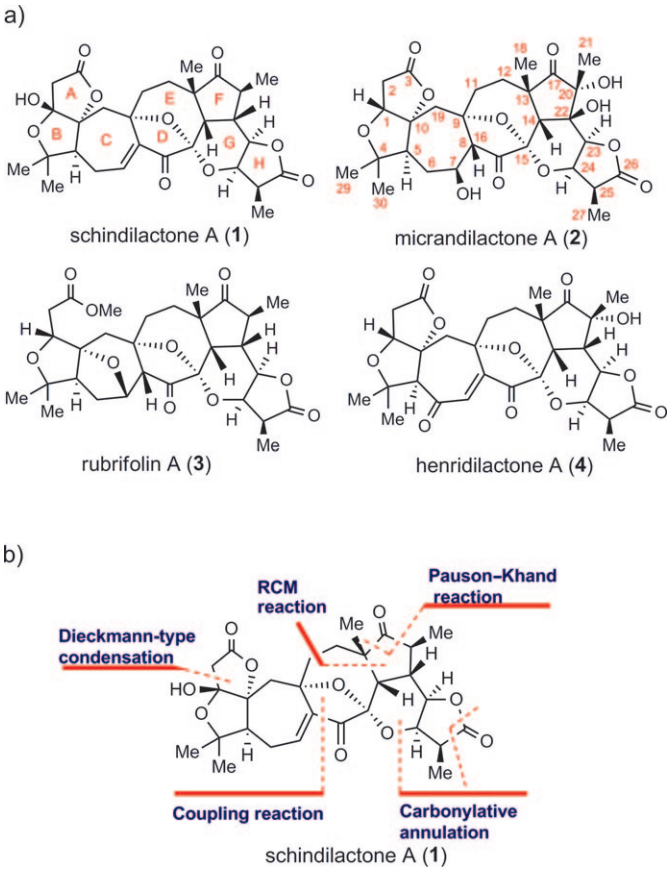
Dedicated to Professor K. C. Nicolaou on the occasion of his 65th birthday

Schindilactone A (**1**)[1] and structures **2**–**4** (Scheme 1a) are representative members of a novel group of nortriterpenoids isolated by Sun and co-workers from the plants of *Schisandraceae*,[2] which have been used in China for the treatment of rheumatic lumbago and related diseases.[3]

Preliminary biological assays indicated that some of them possess biological activities for inhibiting hepatitis, tumors, and HIV-1.[4] The synthetic challenge posed by **1** stems from the complexity of its molecular structure: a highly oxygenated framework bearing 12 stereogenic centers, eight of which are contiguous chiral centers located in the FGH tricyclic ring system, and an oxa-bridged ketal that lies within an unprecedented 7–8 fused carbocyclic core. The structural complexity together with the attractive biological activities has rendered **1** a target for synthetic studies.[5]

Herein we report our efforts on the development of synthetic methods and a strategy centered on the construction of the polycyclic ring system that allowed the first total synthesis of (±)-schindilactone A. This concise strategy opens a pathway for the syntheses of other compounds related to schindilactone A (**2**–**4**, Scheme 1a), as well as their derivatives and analogues.



Scheme 1. a) Naturally occurring nortriterpenoids. b) Strategic bond disconnections of schindilactone A.

Our retrosynthetic analysis of **1** is depicted in Scheme 1b. The key steps are 1) thiourea/palladium-catalyzed carbonylative annulation cascade[6,7] to construct the GH ring system; 2) a thiourea/cobalt-catalyzed Pauson–Khand reaction (PKR)[8] to form the F ring; 3) a ring-closing metathesis (RCM) reaction to make the cyclooctanoid-based ketal of the DE core;[9] 4) a palladium-catalyzed cross-coupling reaction of vinyl bromide with a copper enolate to form the C–C bond between C8 and C16;[10] and 5) a Dieckmann-type condensation[11] to generate the A ring.

Our work began with the diastereoselective synthesis of **12** (Scheme 2). The intermolecular Diels–Alder reaction of **5** with **6** was carried out with Et_2AlCl as the catalyst,[12] and ketone **7** was obtained in 65% yield. Compound **7** was then reacted with MeMgBr in THF to give lactone **8** in 78% yield,

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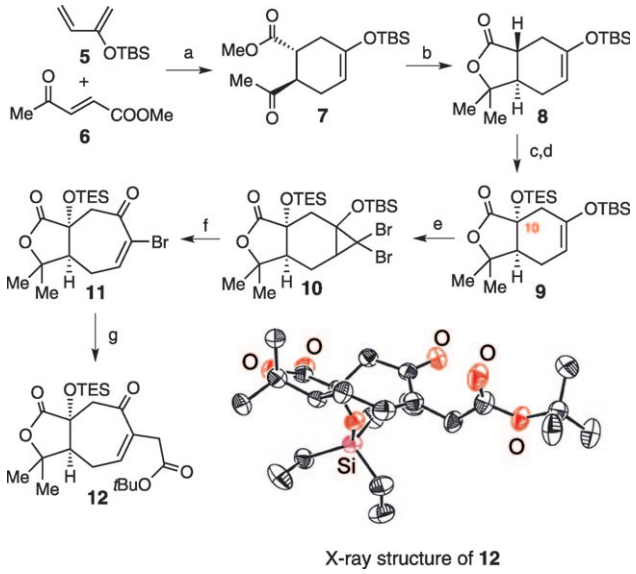
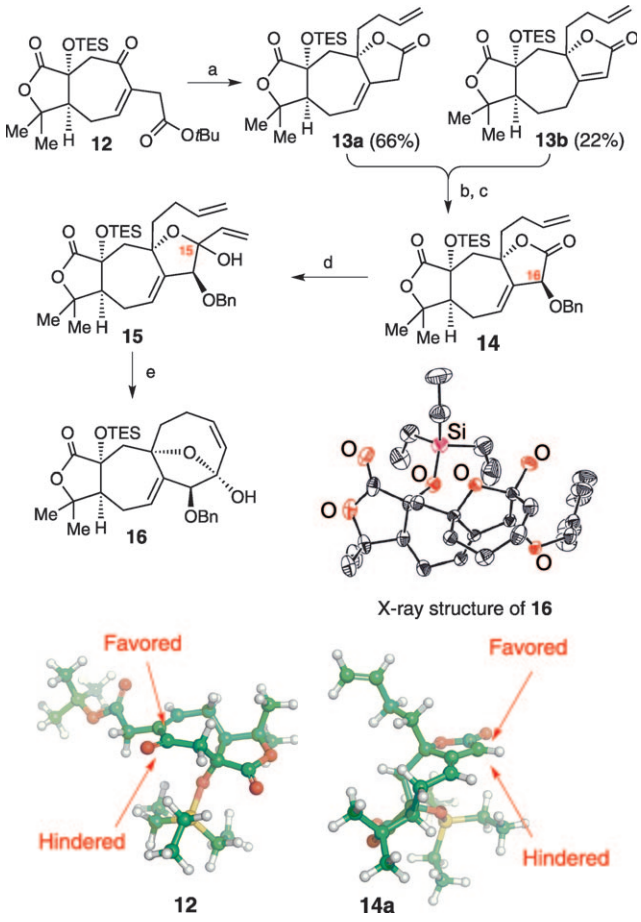


Scheme 2. Synthesis of intermediate **12**. Reagents and conditions: a) **5** (1.5 equiv), **6** (1.0 equiv), Et_2AlCl (1.4 equiv), toluene, 0 °C, 30 min (65 %). b) MeMgBr (1.6 equiv), THF, −78 °C to 0 °C, 1 h (78 %). c) KHMDS (1.5 equiv), THF, −78 °C to 0 °C then $P(OMe)_3$ (1.5 equiv), O_2, 0 °C, 1 h (75 %). d) TESOTf (1.5 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 30 min (95 %). e) KO*t*Bu (3.0 equiv), $CHBr_3$ (3.0 equiv), petroleum ether, −20 °C, 30 min. f) $AgClO_4 \cdot H_2O$ (2.0 equiv), acetone, 30 °C, 10 h (82 % for 2 steps). g) (1-*tert*-butoxyvinyloxy)-(*tert*-butyl)dimethylsilane (3.8 equiv), $PdCl_2/[\{P(o\text{-tol})_3\}_2]$ (0.1 equiv), CuF_2 (4.0 equiv), THF, 75 °C, 24 h (85 %). KHMDS = potassium hexamethyldisilazide, TES = triethylsilyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.



Scheme 3. Synthesis of intermediate **16**. Reagents and conditions: a) But-3-enylmagnesium bromide (3.0 equiv), THF, 0 °C, 30 min (88 %). b) KHMDS (2.5 equiv), THF, −78 °C, then MoOPH (2.0 equiv), −78 °C, 2 h (62 %). c) $BnOC(=NH)CCl_3$ (2.0 equiv), Et_2O, TfOH (cat.), RT, 1 h (65 %). d) Vinylmagnesium bromide (2.5 equiv), THF, 0 °C, 30 min (77 %). e) Grubbs II catalyst (10 mol %), $MgBr_2$ (0.2 equiv), CH_2Cl_2, 30 °C, 6 h (65 %). Bn = benzyl, MoOPH = oxodiperoxomolybdenum (pyridine)(hexamethylphosphoric triamide).

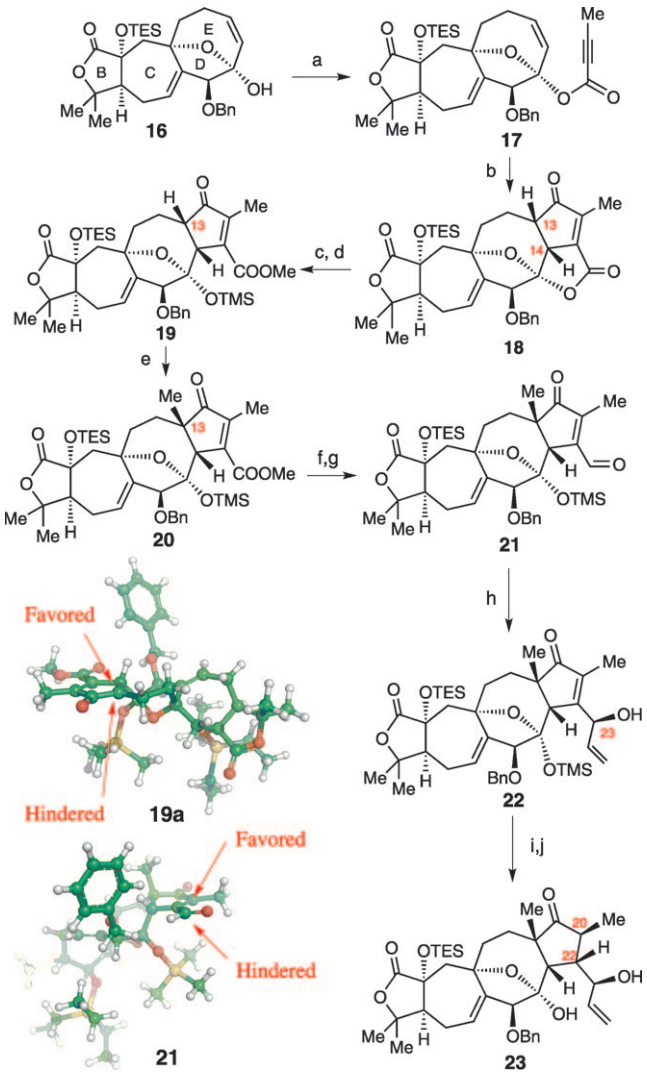
and treatment of **8** with KHMDS in THF and subsequent reaction with O_2 in the presence of $P(OMe)_3$[13] gave a tertiary alcohol in 75 % yield. Thus, vinyl silyl ether **9** was obtained in 95 % yield after reaction of the tertiary alcohol with TESOTf and 2,6-lutidine in CH_2Cl_2.

Cyclopropanation of **9** with dibromocarbene[14] provided **10**, which was subsequently treated with $AgClO_4$[15] in acetone to give vinyl bromide **11** in 82 % yield after two steps. After palladium-catalyzed coupling of **11** with (1-*tert*- butoxyvinyloxy)(*tert*-butyl)dimethylsilane,[16] ketoester **12** was obtained in 85 % yield. The structure of **12** was confirmed by X-ray crystallographic analysis.[31]

With **12** in hand, we then set out to prepare the eight-membered-ring ketal **16**, which is a pivotal target yet challenging for synthesis because of its unfavorable entropic and enthalpic factors arising from the eight-membered ring.[17] To this end, **12** was reacted with but-3-enyl magnesium bromide in THF at 0 °C to diastereoselectively afford lactone **13a**, as well as its regioisomer **13b** in 88 % combined yield. The excellent diastereoselectivity observed in this reaction presumably was attributed to the steric bulk of the OTES group in substrate **12**, which might direct the attack of the Grignard reagent on the ketone from the less hindered face (see the three-dimensional (3D) structure; Scheme 3). The concurrent formation of **13b** could be a result of the double bond isomerization of **13a**.[18] Interestingly, both **13a** and **13b** could be converted into **14** using a sequence involving MoOPH-mediated oxidative hydroxylation[19] and benzylation with $BnOC(=NH)CCl_3$/TfOH.[20] This excellent regio- and diastereoselective α-hydroxylation was presumably due to the steric effect of the OTES group in enolate **14a** (Scheme 3) that was generated in situ by the treatment of **13a** and **13b** with KHMDS in THF.

To prepare **16**, exposure of the resulting lactone **14** to vinyl magnesium bromide[21] at −20 °C gave diene **15** in 77 % yield as a pair of diastereoisomers. Notably, when the diastereoisomers of **15** were treated with a catalytic amount (10 mol %) of the Grubbs II catalyst in the presence of $MgBr_2$ (20 mol %) at 30 °C for 6 hours, **16** was generated as the sole isomer in 65 % yield. This observed $MgBr_2$-mediated in situ epimerization[22] was in line with the results reported by Scholl and Grubbs.[23] The structure of **16** has been established by X-ray crystallographic analysis. [31]

We then moved on to construct **23** (Scheme 4). Inspired by the work of Moyano, Pericàs, and co-workers on the construction of *cis*-fused bicyclo[6.3.0]undecan-1-one through PKR,[24] we envisioned that the oxa-bridged bicyclo-



Scheme 4. Synthesis of intermediate **23**. Reagents and conditions: a) KHMDS (2.0 equiv), but-2-ynoic pivalic anhydride (4.0 equiv), toluene, 0 °C (78 %). b) $[Co_2(CO)_8]$ (0.5 equiv), TMTU (3.0 equiv), PhH, 70 °C, 4 h (74 %). c) MeONa (0.1 equiv), MeOH, RT. d) TMS-imidazole (10 equiv), CH_2Cl_2, RT, 12 h (91 % for 2 steps). e) KHMDS (2.0 equiv), THF, −78 °C then MeI (2.0 equiv), −78 °C (88 %). f) DIBAL (8.0 equiv), CH_2Cl_2, −78 °C. g) DMP (4.0 equiv), $NaHCO_3$ (8.0 equiv), CH_2Cl_2, RT (70 % for 2 steps). h) Vinylmagnesium bromide (2.0 equiv), THF, −78 °C (88 %). i) TBAF (5.0 equiv), AcOH (5.0 equiv), THF, RT (93 %). j) $LiAlH_2(OMe)_2$ (10.0 equiv), THF, −78 °C (60 %). DIBAL = diisobutylaluminum hydride, DMP = Dess–Martin periodinate, TMS = trimethylsilyl.

[6.3.0]undecan-2-one moiety in **18** could be assembled in a *cis*-fused manner by using our thiourea/cobalt-catalyzed PKR[7] of enyne **17**; we anticipated that the butynoic ester in **17** would approach the double bond from the bottom face.

To implement this design, **16** was treated with KHMDS in THF at −78 °C, and the formed potassium alkoxide was then converted into enyne **17** by quenching with but-2-ynoic pivalic anhydride.[25] Thus, under the optimized PKR conditions, **17** was treated with the complex of tetramethyl thiourea (TMTU) and $[Co_2(CO)_8]$ in dry benzene using a balloon of CO at 70 °C for 4 hours, and the desired product **18** was obtained in 74 % yield with the desired stereochemistry at C13 and C14.

We then started investigating methods to install the C13 quaternary carbon center in **20** by methylation. We envisioned that steric bulk around the concave face of substrate **19** through protection of the hydroxy group of the ketal as a silyl ether would guide enolate **19a** (see 3D structure; Scheme 4) to approach MeI from its convex face. Thus, the C13 quaternary carbon center in **20** would be constructed stereoselectively.

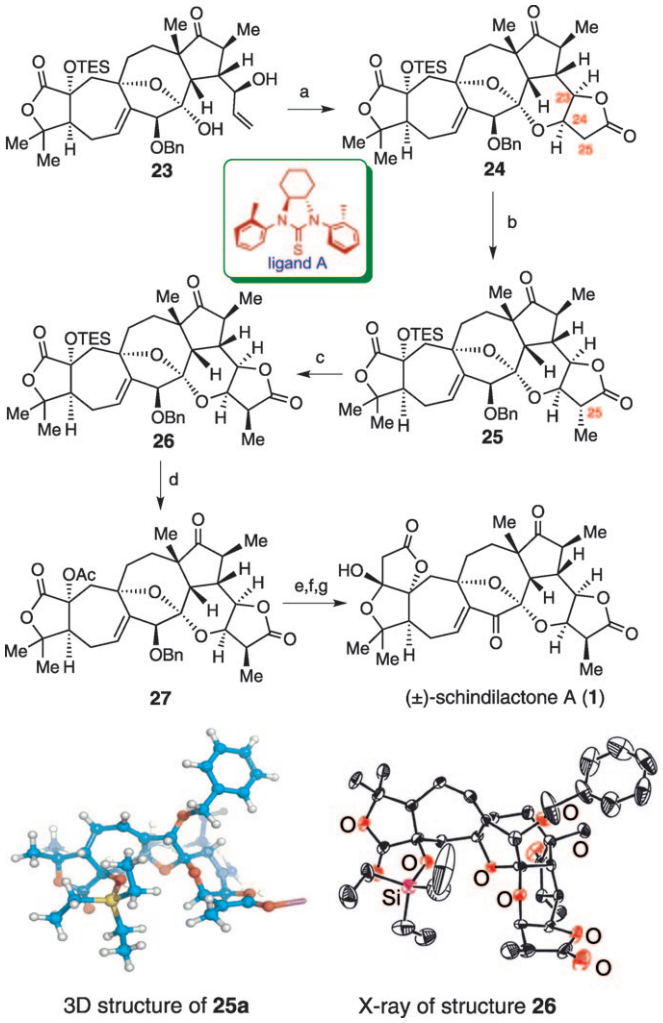
To this end, lactone **18** was converted into its ester **19** in high yield through a methanolysis/silylation protocol. Upon treatment of **19** with KHMDS in THF at −78 °C and subsequent quenching with MeI, product **20** was obtained in 88 % yield as a single diastereoisomer as expected.

Compound **20** was first subjected to DIBAL reduction and subsequent oxidation using DMP to give **21** in 70 % yield over the two steps. Exposure of **21** to vinyl magnesium bromide afforded allylic alcohol **22** as a single isomer in 88 % yield. The excellent diastereoselectivity observed in this reaction is likely attributed to 1) the defined orientation of the aldehyde (resulting from the dipole interaction of the oxygen atom in the aldehyde with the oxygen atom in OTMS), and 2) a steric shielding of the concave face by the OTMS of the substrate **21** (see 3D structure; Scheme 4).

We then sought to install the stereogenic centers C20 and C22 in **23**. To this end, we screened various reducing agents, among which $LiAlH_2(OMe)_2$ turned out to be effective in the hydroxy-group-directed conjugative reduction.[26] In the event, **22** was subjected to desilylation with TBAF in the presence of AcOH to afford a diol, which, upon treatment with $LiAlH_2(OMe)_2$, was converted into **23** as the sole isomer in 60 % yield. This high diastereofacial selectivity was thought to be the result of the hydroxy-group-directed conjugative reduction.

Scheme 5 illustrates how the total synthesis of **1** was completed. On the basis of our prior success of applying the thiourea/palladium catalyzed carbonylative annulation reaction to form the FGH ring system,[27] we planned to use this cascade reaction to stereoselectively form the GH ring system in **24**. In that event, diol **23** was added to a solution of $Pd(OAc)_2$/ligand A in THF under a balloon of CO, and the formed mixture was stirred at 70 °C for 1 hour. To our delight, the lactone **24** was obtained exclusively in 78 % yield, thus demonstrating robustness of the thiourea/palladium catalyzed carbonylative annulation to construct complex molecules with dense functionalities.

The synthesis of **26** was achieved by selective methylation of lactone **24**. Compound **24** was then first treated with LiHMDS in THF at −78 °C to afford an enolate, which upon reaction with MeI[28] gave the methylated product **25** in 80 % yield, however, the newly generated chiral center C25 was opposite to the desired chiral center. Gratifyingly, it was found that the stereochemistry of C25 could be inverted by treatment of **25** with the hindered base lithium 2,2,6,6-tetramethyl-piperidin-1-ide[29] in THF at −78 °C, and subsequent quenching with a saturated solution of NH_4Cl. The structure of **26** was confirmed by X-ray crystallographic analysis.[31] The observed favorable epimerization is believed



Scheme 5. Total synthesis of (±)-schindilactone A (**1**). Reagents and conditions: a) $Pd(OAc)_2$ (0.5 equiv), ligand A (0.5 equiv), $CuCl_2$ (3.0 equiv), CO (atmospheric pressure), THF, 70 °C, 1 h (78%). b) LiHMDS (5.0 equiv), THF, −78 °C, 30 min, then MeI (1.0 equiv), 30 min (80%). c) Lithium 2,2,6,6-tetramethylpiperidin-1-ide (10.0 equiv), THF, −78 °C, 30 min, then a saturated solution of NH_4Cl (76%). d) Ac_2O (10 equiv), $Sc(OTf)_3$ (2.0 equiv), CH_3CN, RT, 1 h. (92%). e) $Pd(OH)_2$, (10% mol%), H_2 (atmospheric pressure), EtOAc, RT, 1.5 h (90%). f) LiHMDS (5.0 equiv), THF, −78 °C to 0 °C, 1 h. g) DMP (3.0 equiv), $NaHCO_3$ (6.0 equiv), CH_2Cl_2, RT, 1 h (60% for 2 steps).

to result from the formation of enolate **25a**, wherein its bottom face was more accessible than its top face, and thereby suited for the subsequent protonation to afford the desired product.

In accordance with our retrosynthetic analysis, we planned to synthesize the A ring through a Dieckmann-type condensation. We fortunately found out that the silyl group in **26** could be directly converted into its corresponding acetyl group in **27** by reaction of **26** with $Ac_2O/Sc(OTf)_3$[30] in CH_3CN.

To complete the total synthesis, **27** was first subjected to hydrogenolysis of the benzyl ether with $Pd(OH)_2$ and H_2 to afford an alcohol in 90% yield, which, upon treatment with LiHMDS in THF at −78 °C proceeded through an intramolecular Dieckmann-type condensation, the product of which underwent an oxidation with DMP to give **1** in 60% yield after two steps. Overall, the synthesis of (±)-schindilactone A consists of 29 steps in its longest linear sequence. The synthetic material has been fully characterized, and its ^1H NMR and ^{13}C NMR spectra are identical to those of the natural product.[1]

In summary, total synthesis of (±)-schindilactone A (**1**) has been accomplished for the first time. The salient features of the synthetic route include: a) an intermolecular Diels–Alder reaction to set up the B ring system; b) a silver-mediated cyclopropane rearrangement to generate the C ring; c) an RCM reaction for the diastereoselective formation of fully the functionalized eight-membered CDE ring system; d) a thiourea/cobalt-catalyzed PKR for the stereoselective construction of the F ring; e) a thiourea/palladium-catalyzed carbonylative annulation for the stereoselective synthesis of the GH ring system; and f) the Dieckmann-type condensation to generate the A ring. The enantioselective total synthesis of other members of the schindilactone A family is currently underway in our laboratories.

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[31] CCDC 830568 (**12**), CCDC 830569 (**16**), and CCDC 830583 (**26**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

