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Model studies toward a synthesis of asperaculin A: exploration of iterative intramolecular Pauson–Khand reaction based strategies to access the dioxa[5.5.5.6]fenestrane framework

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ABSTRACT

A concise strategy, involving tandem intramolecular Pauson–Khand reactions (IPKRs) on a readily available ene-diyne precursor, to access the dioxa-fenestrane framework is delineated.

For nearly a quarter of a century, diterpene laurenene **1** remained the lone example[1] of a fenestrane crafted by nature in which a central carbon shares four rings. This unique reign of laurenene among natural products ended in 2006 when isolation and characterization of a novel sesquiterpenoid penifulvin A **2**[2a] and its sibling secondary metabolites[2b] penifulvins B–E **3**–**6**, all embodying a dioxa[5.5.5.6]fenestrane skeleton, was reported from the cultures of a fungicolous isolate of *Penicillium griseofulvum* NRRL35584, Chart 1. Penifulvin A **2** was shown to exhibit significant insecticidal activity[2a] and this attribute along with the uniquely fascinating dioxa[5.5.5.6]fenestrane architecture present in it held an instant attraction to the synthetic chemists[3] and the endeavors of the Mulzer[4a] group culminated in its first total synthesis in 2009 and of penifulvins B and C in the following year.[4b] More recently, in 2011, research groups[5] from Thailand have reported the isolation and structure determination of a novel dioxa[5.5.5.6]fenestrane based sesquiterpenoid asperculin A **7** (Chart 1) from the mycelial extract of the marine-derived fungus *Aspergillus aculeatus* GRI323-04. Interestingly, both penifulvin A and asperculin A bear dioxa[5.5.5.6]fenestrane core but differ in the substitution and functionalization pattern, particularly in the disposition of oxacyclic segment of the fenestrane frame. As a part of our ongoing interest in the synthesis of penifulvins A–E, we were drawn toward a synthesis of asperculin A **7** and report here a strategy that enables convenient access to the core dioxa[5.5.5.6]fenestrane skeleton **8** (Chart 1) present in this natural product.

Earlier synthesis of fenestranes utilized classical transformations based on aldol chemistry,[3] transannular cationic cyclization,[6] and carbene insertion,[3] intramolecular [2+2] cycloadditions and cyclodehydrations[3] as the key strategic steps. However, in recent years economical and conceptually new approaches based on intramolecular arene-olefin photocycloaddtion,[4a,b,7] transition metal mediated cyclization–carbonylation (like the Pauson–Khand reaction, PKR)[8,9] have proved quite versatile and effective in accessing the fenestrane framework. Among these, the intramolecular Pauson–Khand reaction (IPKR) appeared worthy of further exploitation in generating hetero-fenestrane architecture[9] present in natural products **2**–**7** as it can be implemented on simple and quite readily accessible enyne, diyne, and triyne precursors.

Our initial focus in the context of asperculin A synthesis was to devise a viable route to a functionalized dioxa[5.5.5.6]fenestrane system **8**. For this purpose we began to scout for various precursors which through iterative IPKR protocol could deliver the dioxa[5.5.5.6]fenestrane framework either in a one pot operation or in a stepwise process. A retrosynthetic perspective leading to dioxa-fenestranes **9** and **10** through the intermediacy of **11**–**14** from two key precursors **15** and **16** is depicted in Scheme 1. Interestingly, both the enyne precursors **15** and **16** can be prepared either from glycerol or from D-mannitol.

Synthesis of **15**[10] and **16**[10] from glycerol derived solketal **17** and the corresponding aldehyde **18** was quite straightforward and the successfully executed reaction sequence is displayed in Scheme 2.

In the initial foray toward **9**, we deployed enyne **15** and PKR reaction on it delivered a readily separable mixture of diastereomers **19**[10] and **20**[10] in a ratio of 2.5:1, respectively, Scheme 3. We decided to proceed with the major diastereomer **19** and

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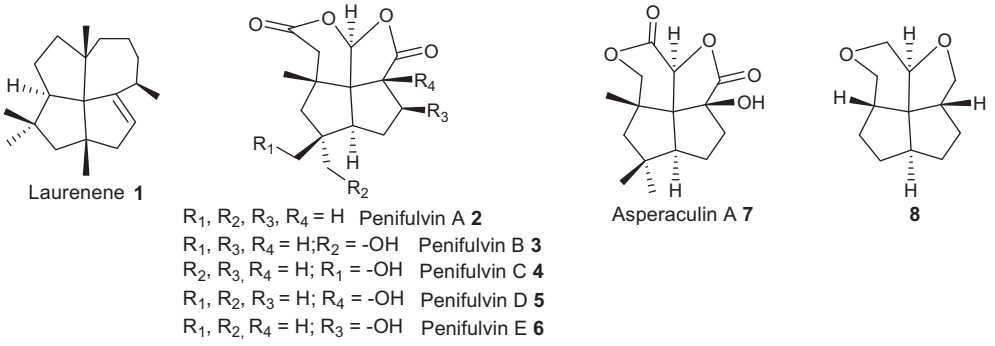
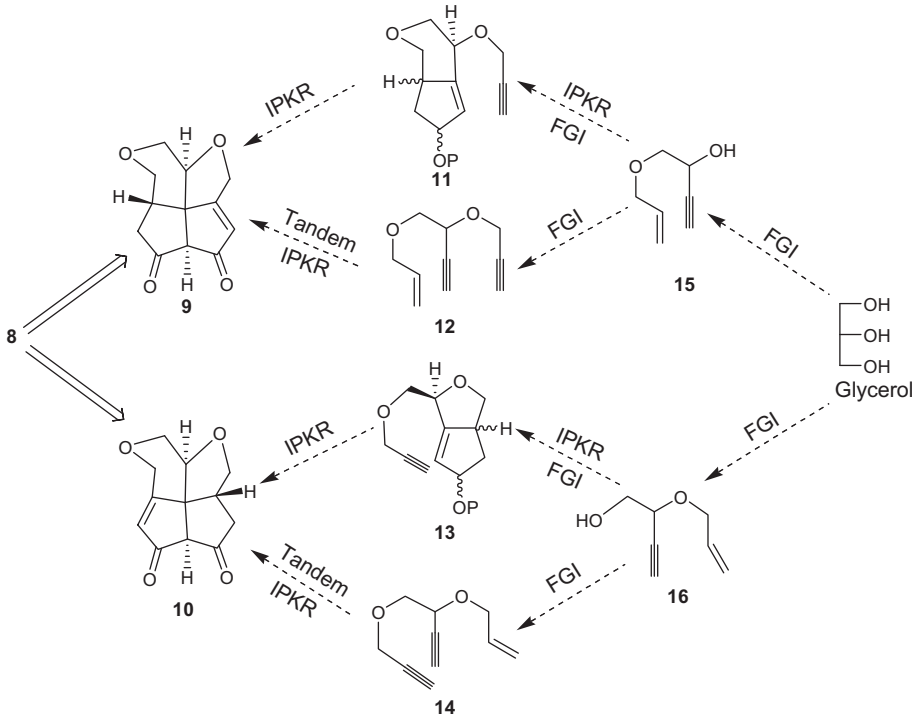
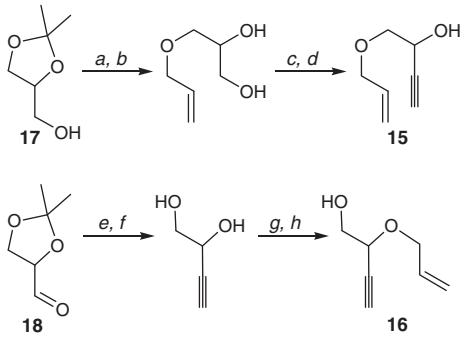


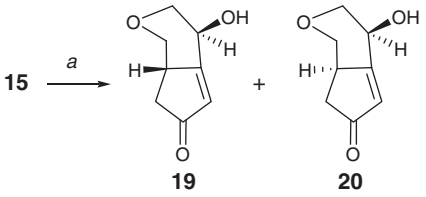
Chart 1. Architecture of fenestranes from nature.



Scheme 1. Retrosynthetic considerations in the assembly of dioxa[5.5.5.6]fenestrane system.



Scheme 2. Reagents and conditions: (a) allyl bromide, ^{t}BuOK, THF, −10 °C to rt, 4 h, quantit.; (b) amberlyst-15 resin, EtOH, reflux, 4 h, 75%; (c) $NaIO_4$, satd aq $NaHCO_3$, DCM, 0 °C to rt, 2 h, 85%; (d) ethynyl magnesium bromide 0.5 M in THF, THF, −60 °C to rt, 2 h, 65%; (e) Ohira–Bestmann reagent, K_2CO_3, MeOH, rt, 12 h; (f) PTSA, MeOH, rt, 12 h, 48% (over two steps); (g) (i) TBSCl, imidazole, DMF, −20 °C, 12 h, 56%; (ii) allyl bromide, ^{t}BuOK, DMF, 60%; (h) TBAF, THF, 0 °C to rt, 1 h, 68%.



Scheme 3. Reagents and conditions: (a) $Co_2(CO)_8$, TMNO, −15 °C to rt, 8 h, 54% (**19**:**20** = 2.5:1).

protected the free hydroxyl group as the bulky TBS group to furnish **21**, Scheme 4. Luche reduction in **21** was diastereoselective (9:1), engendered by the bulky OTBS group and directed hydride addition from the opposite β-face, to furnish **22**. The resultant β-hydroxy group in **22** was differentially protected as PMB derivative **23** and the TBS protection was disengaged to furnish **24**, Scheme 4. Propargylation on **24** proceeded smoothly to deliver **25** and set-up

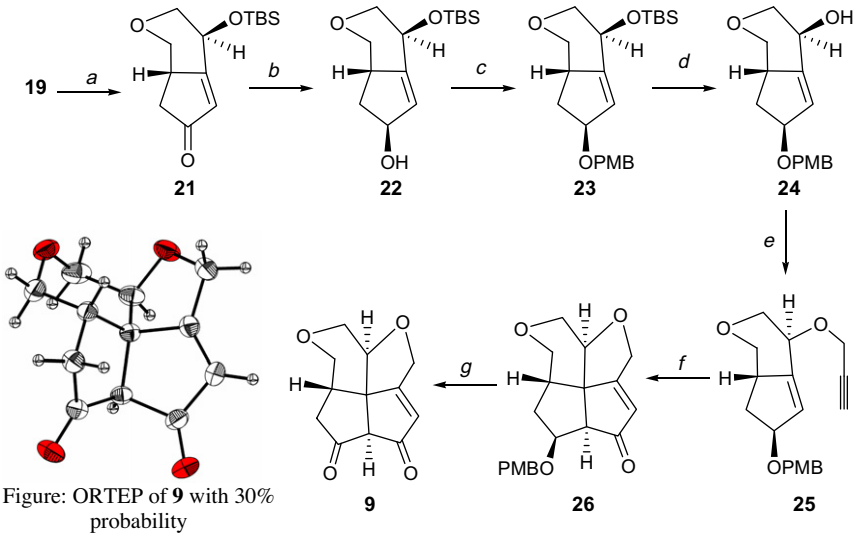


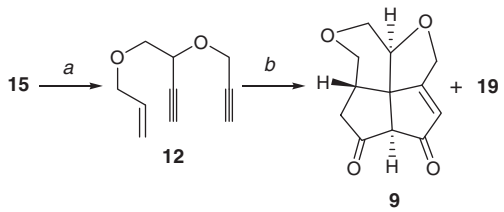
Figure: ORTEP of **9** with 30% probability

Scheme 4. Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 80 °C, 1 h, 90%; (b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, −20 °C, 1 h, 80% (9:1); (c) PMBCl, TBAI, NaH, THF, reflux, 12 h, 75%; (d) TBAF, THF, 0 °C to rt, 1 h, 75%; (e) propargyl bromide, TBAI, NaH, THF, −10 °C to rt, 92%; (f) $Co_2(CO)_8$, TMNO, −15 °C to rt, 5 h, 55%; (g) (i) DDQ, DCM, H_2O, 0 °C to rt, 2–3 h, (ii) DMP, DCM, 0 °C to rt, 60% (over two steps).

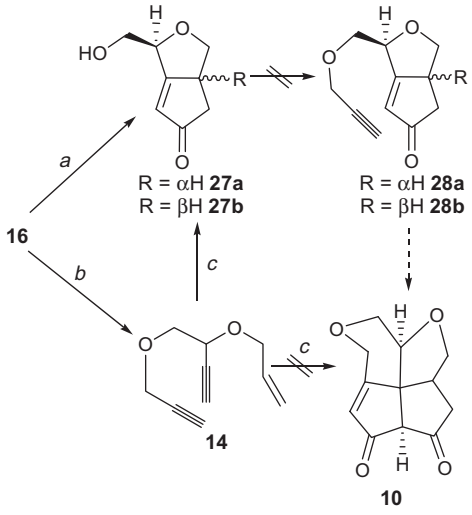
the stage for IPKR. Pleasingly, exposure of **25** to $Co_2(CO)_8$–TMNO under carefully crafted conditions furnished the tetracyclic dioxafenestrane **26** in fair yield, Scheme 4. DDQ mediated deprotection of the PMB protecting group in **26** and Dess–Martin oxidation furnished a crystalline ene-dione **9**[10] bearing the dioxa[5.5.5.6]fenestrane framework corresponding to **8**, Scheme 4. Stereostructure of **9** was secured through a single crystal X-ray structure determination and an ORTP diagram is displayed in (Scheme 4).[11]

Encouraged by the successful construction of the desired tetracyclic framework **9**, we were tempted to construct it through a tandem IPKR in a single pot operation. For this purpose, **15** was propargylated to ene-diyne **12**[10] and subjecting it further to $Co_2(CO)_8$–TMNO milieu led directly to the dioxa[5.5.5.6]fenestrane **9** in 28% yield, Scheme 5. Formation of **9** was a delightful outcome in which four rings and six C–C bonds were formed in a single pot operation and three stereogenic centers were set as required. It may be mentioned that a small amount (10%) of the bicyclic product **19** was also formed alongside **9** during this process indicating that de-propargylation is a debilitating side reaction under the PKR conditions deployed.

Attention was now turned to enyne **16** for further elaboration to the dioxafenestrane system. IPKR reaction on **16** was uneventful and led to a diastereomeric mixture (1:1) of **28a**,**b** which defied separation, Scheme 6. Nonetheless, we decided to proceed further toward **10** (Scheme 1) through propargylation of **28a**,**b** to deliver **29a,b**. However, we were surprised to observe that the seemingly straightforward propargylation of **28a,b** was repeatedly unsuccessful. Disappointed, we turned to **14**[10] which could be obtained from



Scheme 5. Reagents and conditions: (a) propargyl bromide, TBAI, NaH, THF, −10 °C to rt 2 h, 82%; (b) $Co_2(CO)_8$ (2.2 equiv), TMNO(25 equiv), −15 °C to rt, 12 h, **9** (28%), **19** (10%).



Scheme 6. Reagents and conditions: (a) $Co_2(CO)_8$, TMNO, −15 °C to rt, 6 h 28% (**27a**:**27b** = ~1:1); (b) propargyl bromide, TBAI, NaH, THF, −10 °C to rt 2 h, 62%; (c) $Co_2(CO)_8$ (2.2 equiv), TMNO/NMMO (25 equiv), −15 °C to rt, 12 h, 8% (**27a**:**27b** = 1:1).

16 via propargylation to attempt a single pot tandem IPKR. However, several attempts at implementing tandem IPKR on **14** to obtain dioxa-fenestrane **10** proved unsuccessful despite many trials under different reaction regimes. During these efforts, only bicyclic enones **28a,b** could be obtained through initial mono-IPKR reaction and concurrent depropargylation under the reaction conditions (see, vide supra). These observations are in alignment with the earlier findings that point to the marked sensitivity of IPKR reaction to substitution pattern, reaction conditions and in particular to the ability of the propargyl arm to acquire suitable '*exo*' conformation.[9]

In summary, we have successfully and stereoselectively constructed the dioxa-[5.5.5.6]fenestrane core present in the marine natural product asperculin A employing tandem IPKR strategy either in a stepwise manner or in a single pot reaction. The stage is now set for adaptation of this approach toward asperculin A as well as penifulvin A.

Acknowledgments

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10. All new compounds reported here are racemic and characterized on the basis of spectroscopic data (IR, ^{1}H, ^{13}C NMR and mass). Spectral data for some of the key compounds follows: Compound **12** IR (neat) $\bar{\nu}_{max}$ 3294, 2862, 1647, 1091, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95–5.85 (m, 1H), 5.28 (ddd, J = 17, 3, 2 Hz, 1H), 5.18 (ddd, J = 10, 3, 1 Hz, 1H), 4.52 (td, J = 5, 2 Hz, 1H), 4.38 (dd, J = 16, 2 Hz, 1H), 4.31 (dd, J = 16, 2 Hz, 1H), 4.09–4.04 (m, 2H), 3.67–3.62 (m, 2H), 2.48 (d, J = 2 Hz, 1H), 2.44 (t, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.27, 117.45, 79.20, 78.86, 75.34, 74.94, 72.43, 71.86, 67.45, 56.03; HRMS (ES) m/z calcd for $C_{10}H_{12}O_2Na$ (M+Na)$^+$: 187.0735; found: 187.0735; Compound **14** IR (neat) $\bar{\nu}_{max}$ 3924, 2918, 1358, 1097, 935 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91–5.87 (m, 1H), 5.37–5.26 (m, 1H), 5.21 (dd, J = 10, 1 Hz, 1H), 4.35–4.17 (m, 4H), 4.07–4.00 (m, 1H), 3.78–3.68 (m, 2H), 2.47 (d, J = 2 Hz, 1H), 2.45 (t, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.84, 117.87, 79.81, 79.19, 74.84 (2C), 71.70, 69.88, 67.91, 58.65; HRMS (ES) m/z calcd for $C_{10}H_{12}O_2Na$ (M+Na)$^+$: 187.0735; found: 187.0735; Compound **15** IR (neat) $\bar{\nu}_{max}$ 3412, 3296, 1423, 1082, 931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, J = 16, 11, 6 Hz, 1H), 5.28 (dd, J = 17, 1 Hz, 1H), 5.20 (dd, J = 10, 1 Hz, 1H), 4.52 (d, J = 3 Hz, 1H), 4.10–4.03 (m, 2H), 3.61 (dd, J = 10, 4 Hz, 1H), 3.53 (dd, J = 10, 7 Hz, 1H), 2.88 (br s, –OH), 2.45 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.08, 117.80, 81.73, 73.69, 73.34, 72.40, 61.40; HRMS (ES) m/z calcd for $C_7H_{10}O_2Na$ (M+Na)$^+$: 149.0578; found: 149.0579; Compound **16** IR (neat) $\bar{\nu}_{max}$ 3418, 3287, 2932, 1643, 1404, 1188, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00–5.83 (m, 1H), 5.33 (ddd, J = 17, 3, 2 Hz, 1H), 5.23 (ddd, J = 10, 3, 1 Hz, 1H), 4.37–4.26 (m, 1H), 4.21 (td, J = 6, 2 Hz, 1H), 4.05–3.97 (m, 1H), 3.78–3.72 (m, 2H), 2.48 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.89, 118.32, 79.80, 75.37, 70.19, 69.57, 65.27; HRMS (ES) m/z calcd for $C_7H_{10}O_2Na$ (M+Na)$^+$: 145.0578; found: 145.0579; Compound **19** IR (neat) $\bar{\nu}_{max}$ 3402, 1709, 1630, 1093, 979, 858 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (d, J = 2 Hz, 1H), 4.63 (br s, 1H), 4.33 (dd, J = 11, 6 Hz, 1H), 4.22–4.16 (m, 1H), 3.53 (dd, J = 12, 1 Hz, 1H), 3.45–3.38 (m, 1H), 3.07 (t, J = 11 Hz, 1H), 2.72 (br s, –OH), 2.51 (dd, J = 19, 7 Hz, 1H), 1.91 (dd, J = 19, 2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.47, 177.36, 127.40, 74.42, 73.77, 66.09, 37.61, 36.99; HRMS (ES) m/z calcd for $C_8H_{10}O_3Na$ (M+Na)$^+$: 177.0528; found:177.0528; Compound **20** mp 116–118 °C IR (neat) $\bar{\nu}_{max}$ 3356, 1703, 1622, 927, 893 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (t, J = 1 Hz, 1H), 4.61 (t, J = 8 Hz, 1H), 4.30 (dd, J = 10, 6 Hz, 1H), 4.25 (dd, J = 10, 6 Hz, 1H), 3.14 (t, J = 10 Hz, 1H), 3.10–3.03 (m, 1H), 3.03–2.97 (m, 1H), 2.63 (br s, –OH), 2.54 (dd, J = 19, 6 Hz, 1H), 1.99 (dd, J = 19, 2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.51, 182.21, 124.96, 73.39, 73.01, 68.21, 40.98, 36.94; HRMS (ES) m/z calcd for $C_8H_{10}O_3Na$ (M+Na)$^+$: 177.0528; found: 177.0528; Compound **9** mp 192–194 °C IR (thin film) $\bar{\nu}_{max}$ 2924, 1757, 1705, 1643, 1460, 987 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (t, J = 1 Hz, 1H), 4.96 (dd, J = 16, 2 Hz, 1H), 4.73 (d, J = 16 Hz, 1H), 4.28 (d, J = 13 Hz, 1H), 4.03 (dd, J = 12, 5 Hz, 1H), 3.72 (br s, 1H), 3.59 (dd, J = 13, 1 Hz, 1H), 3.13 (br s, 1H), 2.93–2.84 (m, 1H), 2.62–2.51 (m, 2H), 1.92 (dd, J = 16, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.25, 198.42, 185.42, 124.25, 74.49, 68.87, 66.79, 64.93, 61.85, 56.61, 38.48, 32.66; HRMS (ES) m/z calcd for $C_{12}H_{12}O_4Na$ (M+Na)$^+$: 243.0633; found: 243.0653.
11. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 298 K using graphite monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å). The data were reduced by *SAINTPLUS*; the crystal structure was solved by direct methods using *SHELXS-97* and refined by full-matrix least-squares method using *SHELXL-97*. Crystal data for **9**: $C_{12}H_{12}O_4$, M = 220.22, Monoclinic, $P2_1/c$, a = 13.099, b = 9.924, c = 7.861 Å, V = 1010.8 Å^3, α = 90°, β = 98.46°, γ = 90°, Z = 4, ρ_{calcd} = 1.447 mg m^{-3}, 9201 reflections measured, 1755 unique reflections with $I > 2\sigma(I)$. Full-matrix last-squares refinement led to a final R = 0.0403and wR_2 = 0.1073 and GOF = 1.039. CCDC 875386 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.